

MTN 004 Study Specific Procedures Manual

Overview of Section Contents and Identification of Current Section Versions

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments
1	Introduction	3.2	3 June 2009	<ul style="list-style-type: none"> • Updated Figure 1-1, MTN-004 Study Communication, to update Safety Physician contact information. • Updated Section 1.3, Study Activation Process, to include instructions for the MTN site
2	Protocol	3.1	3 June 2009	<ul style="list-style-type: none"> • Inserted Letter of Amendment #01
3	Documentation Requirements	3.2	3 June 2009	<ul style="list-style-type: none"> • Updated Section 3.2, Study Activation Requirements, to include instructions for the MTN site • Deleted Section Appendix 3-2 and renumbered all subsequent appendixes.
4	Participant Accrual	3.1	3 June 2009	<ul style="list-style-type: none"> • Updated study accrual plan to include all three sites • Increased study accrual duration to 14 months • Updated Replacing Participants Section 4.2.7.1 to alert PSRT if any participants require replacement.
5	Informed Consent	3.1	3 June 2009	<ul style="list-style-type: none"> • Updated Section 5.4, Informed Consent for Specimen Storage and Future Research Testing, to instruct sites not to collect storage specimens if the participant did not consent to storage.
6	Participant Follow-Up	3.2	29 June 2009	<ul style="list-style-type: none"> • Updated section 6.3.3, Incomplete Visits, to clarify requirements for completion of baseline web-based questionnaire.
7	Visit Checklists	3.3	30 July 2009	<ul style="list-style-type: none"> • Deleted site-specific visit checklists; included “sample” checklist for all sites • Rearranged pelvic exam procedures so that collection of cervical swabs for cytokine and innate factors testing occurs prior to colposcopic exam.

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Overview of Section Contents and Identification of Current Section Versions

Section Number	Section Title	Current Version Number	Current Version Date	Updates and Comments
8	Participant Retention	3.0	6 Aug 2008	<ul style="list-style-type: none"> • No changes
9	Study Gel Considerations for Non-Pharmacy Staff	3.1	15 Oct 2008	<ul style="list-style-type: none"> • No changes
10	Clinical Considerations	3.4	3 June 2009	<ul style="list-style-type: none"> • Updated collection of colposcopy images to include instructions for Pitt CRS
11	Adverse Event Reporting and Safety Monitoring	3.4	11 Sept 2009	<ul style="list-style-type: none"> • Incorporated Clarification 1 of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, dates August 2009
12	Laboratory Considerations	3.3	29 June 2009	<ul style="list-style-type: none"> • Edited shipping requirements for Pittsburgh site in sections 12.2, 12.4, 12.7.4, 12.7.5, 12.7.6 and Table 12-5. • Updated section 12.5.3: required dipstick urinalysis test • Updated email addresses in Appendix 12-2
13	Behavioral Measures	3.1	3 June 2009	<ul style="list-style-type: none"> • Updated contact information of SCHARP Project Manager
14	Data Collection	3.1	15 Aug 2008	<ul style="list-style-type: none"> • Updated SCHARP study staff
15	Data Communiqués	3.0	6 Aug 2008	<ul style="list-style-type: none"> • No changes
16	Study Reporting Plan	3.0	6 Aug 2008	<ul style="list-style-type: none"> • Updated SCHARP study staff

MTN 004 Study-Specific Procedures Manual (SSP)

Table of Contents

INTRODUCTION.....	1
PROTOCOL.....	2
DOCUMENT REQUIREMENTS.....	3
PARTICIPANT ACCRUAL.....	4
INFORMED CONSENT.....	5
PARTICIPANT FOLLOW-UP.....	6
VISIT CHECKLISTS.....	7
PARTICIPANT RETENTION.....	8
STUDY GEL CONSIDERATIONS FOR NON-PHARMACY STAFF.....	9
CLINICAL CONSIDERATIONS.....	10
ADVERSE EVENT REPORTING AND SAFETY MONITORING.....	11
LABORATORY CONSIDERATIONS.....	12
BEHAVIORAL MEASURES.....	13
DATA COLLECTION.....	14
DATA COMMUNIQUES.....	15
STUDY REPORTING PLAN.....	16

Section 1. Introduction

This section specifies the sources of procedural information available to MTN 004 study staff, the responsibilities of MTN 004 Investigators of Record (IoRs), and the process by which each study site is approved to begin implementation of MTN 004. Also included is information on required submissions to Institutional Review Boards and/or Ethics Committees (IRBs/ECs).

1.1 Sources of Procedural Information

All study procedures must be conducted in accordance with the MTN 004 protocol (see Section 2). The purpose of this manual is to supplement the protocol, not to replace or substitute for it. In the event that this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please alert the MTN Coordinating and Operations Center (CORE) of any such inconsistencies.

Study implementation questions that arise should be managed as follows (see Figure 1-1):

- Questions related to interpretation and proper implementation of the MTN 004 protocol should be directed to the MTN CORE (FHI): Kailazarid Gomez and Lisa Levy.
- Questions related to data collection and management should be directed to the MTN Statistical and Data Management Center (SDMC): Missy Cianciola.
- Questions related to the collection, processing, testing, storage, and/or shipment of laboratory specimens should be directed to the MTN Network Laboratory (NL): Charlene Dezzutti and Edward Livant.
- Questions related to the investigational study products should be directed to the MTN CORE Pharmacist: Cindy Jacobson.
- If questions pertain to more than one topic of protocol interpretation, data collection, laboratory procedures, and/or product, or if you are unsure of who to contact, email the MTN 004 Management Team: mtn004mgmt@mtnstopshiv.org.

Contact information for all other MTN 004 team members can be found in the electronic MTN directory at <http://www.mtnstopshiv.org>.

Figure 1-1: MTN-004 STUDY COMMUNICATION

Protocol Implementation and Procedural Related		
Kailazarid Gomez	919.544.7040 x11282	kgomez@fhi.org
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Data Management Related		
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Laboratory Related		
Ted Livant	412.641.3772	livantew@upmc.edu
Charlene S. Dezzutti	412. 641. 3462	rsicsd@mwri.magee.edu
Product Related		
Cindy Jacobson	412.641.8913	cjacobson@mail.magee.edu
Clinical Management/PSRT Related		
Katherine Bunge	412.917.9936 (pager)	kbunge@mail.magee.edu
Nancy Connolly	206.523.1177	nancycsc@gmail.com
Ross Cranston	412.647.4007	rdc27@pitt.edu

1.2 Investigator Responsibilities

MTN 004 must be conducted in accordance with the United States (US) Code of Federal Regulations and the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (GCP). Copies of these regulations and guidelines are referenced in the MTN Manual of Operations (MOP) which is available at:

<http://www.mtnstopshiv.org>.

The Division of AIDS (DAIDS) Standard Operating Procedures (SOPs) for Essential Documents and Source Documentation are useful for interpreting and operationalizing the applicable regulations and guidelines in accordance with DAIDS expectations. These SOPs are located at: <http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Default.htm>

At each site, MTN 004 also must be conducted in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Each site should file copies of all such regulations, policies, and guidelines in their MTN 004 essential document files (see also Section 3).

The IoR at each study site must sign both a protocol signature page and an FDA Form 1572 to formally indicate his/her agreement to conduct MTN 004 in accordance with the study protocol, applicable US regulations, and MTN policies. A copy of the protocol signature page can be found in the protocol in Section 2 of this manual. The obligations and responsibilities assumed by the IoR when signing the FDA Form 1572 are listed on the form itself, which can be found in Section 3 of the MTN MOP. IoRs may delegate their obligations and responsibilities for conducting MTN 004 to other study staff members, however delegation does not relieve the IoR of his/her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented throughout study implementation.

1.3 Study Activation Process

Prior to undertaking any study procedures, each study site must obtain approval to conduct MTN 004 from all responsible regulatory authorities and IRBs/ECs. The ATN sites must complete protocol registration procedures in compliance with NICHD study activation procedures and receive activation approval from Westat, in conjunction with NICHD and DAIDS, prior to participant screening procedures. The MTN site must complete protocol registration procedures with the DAIDS RCC Protocol Registration Office and receive activation approval from MTN CORE (FHI), prior to participant screening procedures. MTN CORE, SDMC, and NL will assist the sites with activities required for activation. Detailed information on the requirements of these pre-implementation steps can be found in the MTN MOP. Westat will issue a Site-Specific Study Activation Notice for ATN sites and MTN CORE (FHI) will issue a Site-Specific Study Activation Notice for the MTN Site, when all study activation requirements have been met. At each site, no protocol-specified study procedures may be undertaken prior to issuance of the Site-Specific Study Activation Notice.

1.4 IRB/EC Submissions

Figures 1-1 and 1-2 list IRB/EC submission and approval requirements pertinent to MTN 004. Figure 1-1 lists requirements that must be met prior to study initiation. Figure 1-2 lists requirements that must be met during and following study implementation.

Each study site must submit all required documents to all responsible IRBs/ECs; however IRB/EC approval is not required for all documents. Documents requiring approval per US regulations and GCP guidelines are indicated in Figures 1-1 and 1-2. Additional approvals beyond those indicated in the figures may be required by individual IRBs/ECs; in such cases, all required documents must be submitted to and approved by the IRBs/ECs. If your IRB/EC does not require submission of certain documents, this must be documented and filed in your site Essential Document files.

Study sites are encouraged to request an acknowledgement of receipt for all documents submitted to the IRBs/ECs, and to request that the IRBs/ECs note the effective and expiry dates of all approvals. Submissions to your IRB/EC should detail what documents are being forwarded for review. Similarly, replies from your IRB/EC should list the documents that were reviewed and disposition for each document. Procedures for IRB/EC communication must be documented in site-specific SOPs. Documentation of all correspondence to and from all responsible IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in your site Essential Document files.

Figure 1-2
IRB/EC Submissions Required Prior to Initiation of MTN 004

Document	Written Approval Required*
MTN 004 Protocol, Version 1.0 and any subsequent versions (Versions 2.0 and 3.0)	Yes
Informed consent forms: -Screening -Enrollment -Storage and Future Testing of Specimens <i>Note: MTN informed consent forms typically contain information on participant incentive amounts and schedules, however incentives may be approved through submission of separate materials.</i>	Yes
Investigator of Record current CV	No
Investigator's Brochure for SPL7013 Gel (VivaGel™) Document & Version No. : CIB 001-07 ; Release Date : June 20, 2008	No
Participant recruitment materials (prior to use)	Yes
Other written information for study participants (prior to use)	Yes
Other documentation required/requested by the IRB/EC	If required by IRB/EC

*Denotes approvals required by US regulations and GCP guidelines.

Figure 1-3
IRB/EC Submissions Required During and Following Conduct of MTN 004

Document	Written Approval Required*
Study status reports/updates (at least annually)	Yes
Protocol clarification memos (submission encouraged but not required by DAIDS)	No
Protocol amendments (including full amendments (to a new protocol version) and letters of amendment)	Yes
Amended informed consent forms (including forms that are amended due to protocol amendments as well as forms that are amended for site-specific reasons, e.g., to update participant incentive information or to update site contact information) <i>Note: MTN informed consent forms typically contain information on participant incentive amounts and schedules; however incentives may be approved through submission of separate materials. If incentive information is not presented in the informed consent forms, the supplemental materials must be updated, submitted, and approved prior to modification of the incentive amounts or schedules.</i>	Yes
Investigator's Brochure for SPL7013 Gel (VivaGel™) updates	No
New information that may affect adversely the safety of study participants or the conduct of the study (e.g., IND Safety Reports) [§]	No
Reports of adverse events, serious adverse events, and/or events meeting criteria for expedited reporting to DAIDS (per IRB/EC requirements)	No
Protocol departures/deviations/violations (per IRB/EC requirements and/or as directed by DAIDS)	No
Investigator of Record current CV (if Investigator of Record changes during study)	No
Updated/additional participant recruitment materials (prior to use)	Yes
Updated/additional written information for study participants (prior to use)	Yes
Other documentation required/requested by the IRB/EC	If required by IRB/EC
Final study report/closure report	No

*Denotes approvals required by US regulations and GCP guidelines.

[§]Safety information will be distributed by the DAIDS RCC or the MTN CORE. All distributions will include instructions related to IRB/EC submission of the safety information.

Section 2. Protocol

This section contains a complete reference copy of the MTN 004 protocol. At the time of this printing, protocol Version 3.0, dated 30 June 2008; and Letter of Amendment #1, dated 15 May 2009, reflects current protocol specifications.

To ensure that this manual continues to reflect current protocol specifications in the future:

- Upon receipt of any protocol clarification memos, add a copy of the memo to this section.
- Upon receipt of any letters of amendment, add a copy of the letter of amendment to this section.
- Upon receipt of any full protocol amendments, replace the contents of this section with the amended protocol. However, retain the previous version(s) in your MTN 004 essential document file.

Further information on the content and required handling of protocol clarification memos, letters of amendment, and full amendments is available in Section 9 of the MTN Manual of Operations which is available at: <http://www.mtnstopshiv.org>

LETTER OF AMENDMENT #01 TO:

**MTN-004
DAIDS Document ID 10492**

**Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®)
Applied Vaginally in Sexually Active Young Women**

Version 3.0 / 30 June 2008

IND # 62,482

Letter of Amendment Date: 15 May 2009

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the MTN-004 study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their information and review. IRB/EC approval is required before implementation of the revisions contained in this LoA.

The following information will also impact the sample informed consent. Site IRB/ECs are responsible for assessing whether and how the changes included in this LoA are to be communicated to study participants. All IRB/EC requirements must be followed.

Please file this LoA and all associated IRB/EC correspondence in your essential documents files for MTN-004.

Summary of Revisions and Rationale

This LoA adds an additional study site to the MTN-004 protocol. This LoA also clarifies language regarding specimen collection and archive in the Enrollment and Storage and Future Testing of Specimens Sample Informed Consent documents. Changes previously noted in CM # 02, dated October 3, 2007, and CM #03, dated September 3, 2008, are also included in this LoA.

Changes to the Protocol Team Roster are also noted here.

Implementation

This LoA is official MTN-004 protocol documentation. Prior to implementing the revisions listed below, the MTN-004 study sites will submit this LoA to all relevant regulatory authorities and the IRB/EC. Starpharma Pty Ltd, will submit this LoA to the United States Food and Drug Administration for inclusion in Investigational New Drug (IND) application # 62,482. Upon receipt of all required regulatory and IRB/EC approvals, the protocol revisions listed below will be implemented.

With the exception of modifications to the Protocol Team Roster, detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** for additions.

Detailed Listing of Revisions

1. The Protocol Team Roster is updated to reflect updates to the study team.

The following protocol team members have been added to the roster:

Beatrice Chen, MD, MPH

Site Investigator

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300 Halket Street, Suite 5414
Pittsburgh, PA 15213
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Missy Cianciola, MS

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The following protocol team members have updated roster information:

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The following listings are deleted from the Protocol Team Roster: Pat Farrell, Pamina Gorbach, Corey Kelly and Karen Patterson.

2. As previously noted in CM #03, Sections 6.2.6, 7.6.3, and 8.3.1 are updated.

In Section 6.2.6, Retrieval of Unused Study Products, third and fourth sentences are updated:

All unused study products must be returned **by the participant** to the site, **placed in a biohazard container** and then **destroyed at the site**. **Unused study product remaining in the pharmacy must be** forwarded to the MTN CORE **pharmacist for destruction** after the study is completed or terminated unless otherwise instructed by the MTN CORE.

In Section 7.6.3, Enrollment Visit, Table 13: Enrollment Visit, Study Supplies row, is updated to maintain consistency with Version 3.0 of the protocol:

Study Supplies	<ul style="list-style-type: none"> • Dispense two cartons (20 applicators) of study gel, male condoms and panty liners, and/or pads, and resealable plastic bags • Participant to insert first dose in study clinic
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In Section 8.3.1, Adverse Events, fourth paragraph, second sentence is deleted and fourth sentence modified to omit AE reporting for male partners:

Second sentence

~~Participants will be encouraged to report to the study clinician any problems experienced by their male partners that might be potentially related to study product.~~

Fourth sentence

~~Study site staff will document on study CRFs all AEs reported by or observed in enrolled study participants or their partners from the time of their first dose of study gel through the Three-Week Clinic Visit or early termination, regardless of severity and presumed relationship to study gel or applicators.~~

3. Throughout the protocol, text is updated to reflect the addition of a new study site.

In the Schema, participating sites, study design, and study duration are updated:

Participating Sites:

- University of South Florida, Tampa, Florida
- University of Puerto Rico, San Juan, Puerto Rico
- **Pitt CRS, Pittsburgh, Pennsylvania**

Study Design: Phase 1, three arm, ~~two-three~~ site, randomized, double blind, placebo-controlled trial comparing VivaGel[®], VivaGel[®] placebo, or HEC placebo gel (HEC Gel) applied vaginally twice daily for 14 days

Study Duration: Approximately 21 days per participant, ~~nine~~ **fourteen** calendar months of accrual, and ~~ten~~ **fifteen** months total planned study duration

In Section 1.4, Study Investigators is updated:

Site Investigator: Beatrice Chen, MD MPH
Site Investigator
Magee-Womens Hospital of UPMC
300 Halket Street, Suite 5414
Pittsburgh, PA 15213 USA

In Section 4.1, Identification of Study Design, first and last sentences are updated:

MTN-004 is a ~~two~~**three** site, Phase I, double blind, randomized, controlled comparison with 14 days of twice daily exposure to VivaGel[®], VivaGel[®] placebo, or HEC gel, and follow-up among HIV-uninfected sexually active women. Participants in all three arms will receive male condom counseling and free male condoms on an ongoing basis. The study will be conducted at ~~two~~**three** sites: University of South Florida, ~~and~~University of Puerto Rico, **and the Pitt CRS.**

In Section 4.4, Time to Complete Enrollment is updated:

The approximate time to complete study enrollment is expected to be ~~nine~~**fourteen** months.

In Section 4.6, Sequence and Duration of Trial Periods, Table 9, Projected Sequence and Duration of Trial Periods for MTN-004, Version 3.0, is updated:

Enrollment Period	Follow-Up Period	Total Duration
9 14 months	1 month	10 5 months

In Section 4.8, Sites, the number of participating sites is updated:

~~Two~~**Three** study sites are planned for this trial: University of South Florida, ~~and~~University of Puerto Rico, **and Pitt CRS.**

In Section 5.1, Selection of the Study Population, second paragraph, second and third sentences are updated:

Participants will be recruited from a variety of venues. There are ~~two~~**three** sites: University of South Florida, ~~and~~University of Puerto Rico, **and Pitt CRS.** ~~Each site will enroll approximately 30 participants.~~ **A total of approximately 61 participants will be enrolled among the three sites.** Additional participants may be enrolled if non-adherent participants need to be replaced. ~~or if enrollment “slots” need to be shifted from one site to another.~~

In Section 5.1.2, Recruitment, first and third sentences are updated:

Members of the research teams at ~~both~~**all** study sites will recruit women from various clinical sites at which they are providing direct patient care to potential study participants. Study staff will contact volunteers from previous research studies if those participants have previously signed an authorization permitting this type of contact. Site IRB-approved media advertisements, telephone scripts, and fliers will be used. These materials will be

presented and discussed with the community advisory boards at ~~both~~**all** sites before submission to the local IRBs. Written informed consent will be obtained prior to the initiation of any study-related procedures.

In Section 6.4.4, Required Medications and Procedures, second paragraph, Male Condoms subsection, first sentence is updated:

~~Both~~**S**tudy site pharmacies will be provided with a single brand of lubricated male condoms by MTN CORE to distribute to participants in quantities expected to be sufficient according to study-specific procedures when study product is dispensed.

In Section 6.4.4, Required Medications and Procedures, third paragraph, Panty Liners and Pads subsection, first sentence is updated:

~~Both~~**S**tudy site pharmacies will be provided with single brands of panty liners and pads by the MTN CORE to distribute to participants in quantities expected by the participant to be sufficient when study product is dispensed.

Section 7.4.3.1 Quality Control and Quality Assurance Procedures is updated:

Network Laboratory staff will conduct visits as needed to ~~both~~**all** sites to assess the implementation of on-site laboratory quality control procedures, including the proper maintenance of laboratory testing equipment, etc.

In Section 7.7, Colposcopy, first sentence is updated:

Experienced staff at ~~both~~**all three** sites will conduct colposcopic examinations of the study participants. In addition, an MTN Safety Physician will provide specialized training in colposcopy for the evaluation of vaginal products.

In Section 8.1, Safety Monitoring, first sentence is updated:

A sub-group of the Protocol Team, including the MTN Safety Physicians, the MTN PI, MTN-004 Protocol Chair, MTN Protocol Specialist, Statistical Data Management Center (SDMC) Clinical Affairs Research Nurse, SDMC Project Manager, ~~both~~**all** Site PIs, FHI Protocol Coordinator, DAIDS and NICHD Medical Officers, and DAIDS Clinical Operations Study Coordinator, will serve as the Protocol Safety Review Team (PSRT).

In Section 8.3.1, Adverse Events, first paragraph, third sentence is updated:

This definition will be applied to ~~both~~**all** treatment arms.

Section 10.1, Overview and General Design, is updated:

This is a ~~two~~**three** site, Phase I, double blind, randomized, controlled comparison with 14 days of twice daily exposure to VivaGel[®], VivaGel[®] placebo, or HEC gel, and follow-up among HIV-uninfected sexually active women.

In Section 10.9, Participant Accrual and Follow-Up, fourth sentence is updated:

Accrual is anticipated to take approximately 9-14 months. Monthly accrual targets will be available in the SSP.

4. Throughout the protocol, text is updated for applicability to MTN sites, in addition to ATN sites.

Section 1.2, Sponsor and Monitor Identification, is updated to reflect PPD as the monitor for DAIDS sites:

**Monitor: PPD, Inc.
929 North Front Street
Wilmington, NC 28401-3331 USA**

In Section 12, Clinical Site Monitoring, first paragraph is updated to reflect PPD as the monitor for DAIDS sites:

Study monitoring **for the Tampa and San Juan sites** will be carried out by Westat (Rockville, MD), **and by PPD, for the Pitt CRS**. On-site study monitoring will be performed in accordance with DAIDS policies. Site monitoring visits will be conducted to assess compliance with Health and Human Services (HHS) Regulations 45 CFR Part 46 and 21 CFR Parts 50, 56, and 312. Study monitors will visit the site to:

In Section 13.5, Participant Confidentiality, first paragraph, first and second sentences, and second paragraph, first and second sentences are updated:

Members of the study staff **at all sites** are ~~all~~ trained in patient confidentiality for their participation in ~~the ATN~~**MTN-004**. ~~The only sites at which this study will be performed are both ATN Trials Units (ATU).~~ The log of study participant names and other protected health information will be kept in a double-locked area. All computer information about study volunteers will be kept on a computer with log-on passwords. Laboratory specimens are labeled with study numbers and date, and are delivered or shipped by study staff. The study sites' data management and clinical staff are the only personnel with access to the protected health information of study volunteers. Each member of the staff has log-on identification and password, logs off before leaving a computer screen unattended, and closes their office door when out of the office. All research records will be kept indefinitely following closure of this study.

To further protect the privacy of the study participants, the ATN has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). **The MTN has also obtained a Certificate of Confidentiality which applies to MTN sites.** With this Certificate in place, ~~the ATN~~ researchers cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study participant.

Section 13.2, Protocol Registration is updated to reflect protocol registration for the Pitt CRS.

A subheading is added to the original language in Section 13.2 to clarify the separate protocol registration procedures for the University of South Florida and the University of Puerto Rico:

Protocol Registration for the University of South Florida and the University of Puerto Rico

The text for protocol registration for the University of South Florida and the University of Puerto Rico remains unchanged.

A separate protocol registration subsection is added for Pitt CRS:

Protocol Registration for Pitt CRS

The study site will complete protocol registration with the DAIDS RCC Protocol Registration Office. For additional information, refer to the protocol registration documents located at <http://rcc.tech-res.com/forms.htm>. Protocol registration must occur as a condition for site-specific study activation; no participants may be screened or enrolled in this study prior to obtaining protocol registration approval and completing all other study activation requirements. MTN CORE (FHI) staff will notify the study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chairs and the NIAID Medical Officer and NICHD Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s) and the RCC prior to implementing the amendment.

5. The Sample Informed Consent documents are updated to reflect changes to the study sites, anticipated duration of the study, clarify language related to the collection and long-term storage of plasma archive specimens, and to include modifications previously made in CM #02, dated October 3, 2007.

The following changes have been made to Appendix V: Sample Informed Consent document (Screening):

In the Why Are These Screening Exams and Tests Being Done? subsection, fourth paragraph, second, third, and fourth sentences are updated:

A total of approximately 61 women from Florida, ~~and Puerto Rico,~~ **and Pennsylvania** will join this study (~~about 30 in Florida, and about 30 in Puerto Rico~~). ~~About 30 women will be in the study here at [INSERT NAME OF SITE].~~ The whole study will take about ~~ten~~ **fifteen** months to finish.

The following changes have been made to Appendix VI: Sample Informed Consent document (Enrollment):

In the Why is this Study Being Done? subsection, fifth paragraph, second, third, and fourth sentences are updated:

A total of 61 women from Florida, ~~and Puerto Rico,~~ **and Pennsylvania** will join this study (about 30 in Florida, ~~and about 30 in Puerto Rico~~). ~~About 30 women will be in the study here at [INSERT NAME OF SITE].~~ The whole study will take about ~~ten~~ **fifteen** months to finish.

In the What Do I Have To Do If I Am In This Study? Enrollment subsection, the second bullet is updated:

- Give blood for tests to check on the health of your blood cells, liver, and kidneys and to confirm that there is no SPL7013 already in your blood (about 30 mL or about 2 tablespoons). **If you consent to the long-term storage of specimens, a portion of this blood sample will be stored for potential future testing.**

As previously noted in CM #02, Telephone Call subsection, the first sentence is modified:

Two **to four** days after you have your Enrollment Visit, you will have a phone call with study staff to talk about any problems you might have with the gel applicator.

As previously noted in CM #02, One-Week Clinic Visit subsection, the sixth bullet is omitted:

- ~~Complete a computerized questionnaire about your use of the study gel.~~

In the How Many Women Will Take Part in this Study? subsection, the second sentence is updated:

Approximately 61 women will take part in this study. ~~About 30 women will be from Florida, and about 30 women will be from Puerto Rico.~~

In Appendix VII: Sample Informed Consent Document (Storage and Future Testing of Specimens), How Will You Get The Samples From Me? subsection is modified:

The research doctors want to **collect and** save ~~any extra~~ blood and cervical fluid ~~leftover from your tests~~ during the study. This ~~leftover~~ blood and cervical fluid **(including any leftover specimens)** will be kept and used for future research.

MTN-004
Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®)
Applied Vaginally in Sexually Active Young Women

A Study of the Microbicide Trials Network

In Cooperation with:
Adolescent Medicine Trials Network for HIV/AIDS Interventions

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
US National Institutes of Health

Grant #:
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DAIDS Protocol #:
10492

Starpharma Protocol #:
SPL7013-006

Co-Sponsored by:
Starpharma Pty Ltd

IND # 62,482

Protocol Chair:
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Version 3.0
30 June 2008

MTN-004

**Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®)
Applied Vaginally in Sexually Active Young Women**

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS.....vi

PROTOCOL TEAM ROSTERviii

SCHEMA.....xi

1 KEY ROLES..... 14

 1.1 Protocol Identification..... 14

 1.2 Sponsor and Monitor Identification..... 14

 1.3 Medical Officers 14

 1.4 Site Investigators 15

 1.5 Clinical Laboratories 15

 1.6 Data Center..... 16

 1.7 Study Operations 16

2 INTRODUCTION..... 17

 2.1 HIV/AIDS Prevention and Microbicides..... 17

 2.2 The MTN Research Agenda 17

 2.3 Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN)..... 17

 2.4 SPL7013 18

 2.5 Condom Integrity..... 20

 2.6 Anti-HSV Activity..... 20

 2.7 Anti-HIV-1 Activity 20

 2.8 *In vitro* Studies 21

 2.9 Animal Studies 22

 2.10 Clinical Studies 26

 2.11 VivaGel® Placebo..... 28

 2.12 HEC Gel..... 31

 2.13 Anti-HSV Activity..... 31

 2.14 Anti-HIV-1 Activity 31

 2.15 *In Vitro* Studies..... 32

 2.16 Animal Studies 32

 2.17 Clinical Studies 33

 2.18 Study Hypothesis and Rationale 34

3 OBJECTIVES..... 36

 3.1 Primary Objective..... 36

 3.2 Secondary Objectives 36

 3.3 Exploratory Objectives 37

4 STUDY DESIGN 37

 4.1 Identification of Study Design..... 37

 4.2 Summary of Major Endpoints..... 37

 4.3 Description of Study Population 38

 4.4 Time to Complete Enrollment..... 38

 4.5 Study Groups 39

 4.6 Sequence and Duration of Trial Periods 39

4.7	Expected Duration of Participation	39
4.8	Sites	39
5	STUDY POPULATION	40
5.1	Selection of the Study Population	40
5.2	Inclusion Criteria	41
5.3	Exclusion Criteria	42
6	STUDY PRODUCT	43
6.1	Regimen.....	43
6.2	Study Product Supply and Accountability	44
6.3	Assessment of Participant Adherence	45
6.4	Concomitant Medications and Procedures	46
7	STUDY PROCEDURES.....	47
7.1	Clinical Evaluations and Procedures.....	47
7.2	Behavioral Measures	48
7.3	Laboratory Evaluations	49
7.4	Specimen Collection and Processing.....	49
7.5	Specimen Preparation, Handling, and Shipping.....	52
7.6	Sequence of Procedures/Evaluations	52
7.7	Colposcopy	61
7.8	Colposcopic Images.....	61
7.9	Final Contact.....	61
8	ASSESSMENT OF SAFETY.....	61
8.1	Safety Monitoring	61
8.2	Clinical Data Safety Review	62
8.3	Adverse Events Definitions and Reporting Requirements	63
8.4	Expedited Adverse Event Reporting Requirements	65
8.5	Local Regulatory Requirements.....	67
9	CLINICAL MANAGEMENT	67
9.1	Toxicity Management.....	67
9.2	Other Disease Events	68
9.3	Pregnancy.....	68
9.4	Criteria for Discontinuation of Study Product, and Discontinuation of Study Participation.....	69
10	STATISTICAL CONSIDERATIONS.....	70
10.1	Overview and General Design	70
10.2	Study Endpoints.....	70
10.3	Study Hypothesis	71
10.4	Sample Size.....	71
10.5	Randomization Procedures.....	72
10.6	Justification for Placebo Gels.....	73
10.7	Blinding	73
10.8	Maintenance of Trial Randomization Codes	73
T10.9	Participant Accrual and Follow-Up	73
10.10	Data and Safety Monitoring and Analysis.....	74
11	DATA HANDLING AND RECORDKEEPING.....	76
11.1	Data Management Responsibilities.....	76

11.2	Source Documents and Access to Source Data/Documents	76
11.3	Quality Control and Quality Assurance	76
11.4	Study Coordination	77
12	CLINICAL SITE MONITORING	77
13	HUMAN SUBJECTS PROTECTIONS	78
13.1	Institutional Review Boards	78
13.2	Protocol Registration	78
13.3	Risk/Benefit Statement	79
13.4	Informed Consent Process	80
13.5	Participant Confidentiality	81
13.6	Special Populations	81
13.7	Incentives	82
13.8	Communicable Disease Reporting	82
13.9	Access to HIV-Related Care	82
13.10	Study Discontinuation	83
14	PUBLICATION POLICY	83
	APPENDICES	84
	APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS	84
	APPENDIX II: OUTCOMES, DIAGNOSTICS, AND FOLLOW-UP EVALUATIONS	85
	APPENDIX III: HIV ANTIBODY TESTING ALGORITHM	87
	APPENDIX IV: MANUAL FOR EXPEDITED REPORTING OF ADVERSE EVENTS TO DAIDS	88
	APPENDIX V: SAMPLE INFORMED CONSENT DOCUMENT (SCREENING)	98
	APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)	107
	APPENDIX VII: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)	121
	REFERENCES	125

TABLE OF FIGURES

Table 1:	VivaGel [®] Formulation	19
Table 2:	Effects of SPL7013 Gels on Vaginal Transmission of SHIV _{89.6P} in Macaques	21
Table 3:	Design of First Clinical Study in Women	26
Table 4:	Reported AEs Possibly Related to Study Treatment	27
Table 5:	VivaGel [®] Placebo Formulation	29
Table 6:	HEC Gel Formulation	31
Table 7:	Study Design	37
Table 8:	Sequence and Duration of Trial Periods for Individual Participants	39
Table 9:	Projected Sequence and Duration of Trial Periods for MTN-004 Version 3.0.	39
Table 10:	Study Product Regimen	43
Table 11:	Screening 1 Visit	53
Table 12:	Screening 2 Visit	54
Table 13:	Enrollment Visit	55
Table 14:	One-Week Clinic Visit	57
Table 15:	Two-Week Clinic Visit	58
Table 16:	Three-Week Clinic/Early Termination Visit	59

Table 17: Analysis of Adverse Event Frequency with n = 18	72
Table 18: Analysis of Adverse Event Frequency with n = 21	72

MTN-004

Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine transaminase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
ATU	ATN Trials Units
BV	bacterial vaginosis
BUN	blood urea nitrogen
CBC	complete blood count
CFR	code of federal regulations
cGMP	current Good Manufacturing Practices
CONRAD	Contraceptive Research and Development Organization
CPST	Center for Pharmaceutical Science and Technology
CRF	case report form
CT	Chlamydia trachomatis
DAIDS	Division of AIDS
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
DOC	Data and Operations Center (Westat)
EAE	expedited adverse event
EDTA	ethylenediaminetetraacetic acid
FDA	(United States) Food and Drug Administration
FHI	Family Health International
GC	Neisseria gonorrhoea
GCP	Good Clinical Practices
GRAS	Generally Recognized As Safe
HEC	Hydroxyethylcellulose
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HSV-1, HSV-2	Herpes Simplex Virus type 1, type 2
IATA	International Air Transport Association
IC ₅₀	half maximal inhibitory concentration
ICH	International Conference on Harmonization
ID ₅₀	intravaginal dose
IRL	Industrial Research Limited
IWGM	International Working Group on Microbicides
IND	investigational new drug
IRB	Institutional Review Board
IUD	intrauterine device
KOH	potassium hydroxide
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantification

LIST OF ABBREVIATIONS AND ACRONYMS (Continued)

µg	microgram
mg	milligram
mL	milliliter
MOP	Manual of Procedures
MTN	Microbicide Trials Network
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
N	number
N-9	Nonoxynol-9
NIAID	National Institute of Allergy and Infectious Disease
NICHHD	National Institute of Child Health and Development
NIH	National Institutes of Health
nM	nanomolar
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NOEL	no-observed-effect-level
PAB	DAIDS Pharmaceutical Affairs Branch
PAMA	Pediatric, Adolescent and Maternal AIDS
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PI	Principal Investigator
PID	pelvic inflammatory disease
PSRT	Protocol Safety Review Team
PTID	Participant Identification
qs	<i>quantum sufficit</i> ; a sufficient quantity
RBC	red blood cell
RCC	Regulatory Compliance Center
RNA	ribonucleic acid
RPR	rapid plasma reagin
RT	reverse transcriptase
RTI	reproductive tract infection
SADR	serious adverse drug reaction
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDA	strand displacement assay
SDMC	Statistical Data Management Center
SHIV	Simian-Human Immunodeficiency Virus (SIV/ HIV hybrid virus)
SLPI	secretory leukocyte protease inhibitor
SOP	standard operating procedure(s)
SSP	study specific procedure(s)
STD	sexually transmitted disease
STI	sexually transmitted infection
STICTG	Sexually Transmitted Infections Clinical Trials Group
ULN	upper limits of normal
UNAIDS	Joint United Nations Program on AIDS
WB	Western blot
WBC	white blood cell
w/w	weight for weight

MTN-004

Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

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MTN-004

**Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®)
Applied Vaginally in Sexually Active Young Women**

INVESTIGATOR SIGNATURE FORM

Version 3.0

30 June 2008

A Study of the Microbicide Trials Network (MTN)

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
US National Institutes of Health

Co-Sponsored by:

Starpharma Pty Ltd

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study gel for the indication in which it was studied, unless otherwise specified by the Division of AIDS (DAIDS), Starpharma Pty Ltd, or the Microbicide Trials Network (MTN) Coordinating and Operations Center. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the U.S. Food and Drug Administration (FDA) is notified that the Investigational New Drug application (IND) is discontinued. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, and Starpharma Pty Ltd for review prior to submission.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Investigator of Record

Signature of Investigator of Record

Date

MTN-004

Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

SCHEMA

Short Title: Safety and Acceptability of VivaGel® in Sexually Active Women

Clinical Phase: 1

IND Sponsor: Starpharma Pty Ltd

Protocol Chair: Ian McGowan, MD, PhD, FRCP

Sample Size: Approximately 61 women, including 7 participants enrolled under Version 2.0 of the MTN-004 protocol

Study Population: US sexually active, HIV-negative women between the ages of 18 and 24 years with a normal genital tract

Participating Sites:

- University of South Florida, Tampa, Florida
- University of Puerto Rico, San Juan, Puerto Rico

Study Design: Phase 1, three arm, two site, randomized, double blind, placebo-controlled trial comparing VivaGel®, VivaGel® placebo, or HEC placebo gel (HEC Gel) applied vaginally twice daily for 14 days

Study Duration: Approximately 21 days per participant, nine calendar months of accrual, and ten months total planned study duration

Study Regimen:

Arm	Description	N	Frequency
1	VivaGel®	*18	Twice daily for fourteen consecutive days
2	VivaGel® placebo	*18	Twice daily for fourteen consecutive days
3	HEC gel	18	Twice daily for fourteen consecutive days

*Arms 1 and 2 will each have a final N between 18 and 25.

Primary Objective:

- To assess the safety of VivaGel® when administered for 14 consecutive days on the vulvar and cervicovaginal mucosa of healthy sexually active HIV-negative women aged 18-24 years

Primary Endpoints:

- Abnormal genital symptoms judged by the Investigator to be possibly, probably, or definitely related to product use
- Abnormal pelvic exam findings (excluding abnormal findings observed by colposcopy only) judged by the Investigator to be possibly, probably, or definitely related to product use
- Grade 3 or higher laboratory values (as defined by the DAIDS Toxicity Tables) for hematology, liver function, creatinine level and coagulation judged by the Investigator to be possibly, probably, or definitely related to product use
- Adverse experiences judged by the Investigator to be possibly, probably, or definitely related to product use

Secondary Objectives:

- To assess the adherence to a short-term regimen of VivaGel® among healthy sexually-active HIV-negative women aged 18-24 years
- To evaluate product acceptability among healthy sexually-active HIV-negative women aged 18-24 years
- To assess the effect of a twice daily short-term regimen of VivaGel® on the vaginal microflora of healthy sexually-active HIV-negative women aged 18-24 years

Secondary Endpoints

Consistent with the secondary study objectives to assess adherence to, and acceptability of, a short-term regimen of VivaGel®, and to assess the effect of this regimen on vaginal microflora, the following endpoints will be assessed:

- The proportion of participants who report via adherence questionnaire that they were adherent to the product use regimen, with adherence defined as the application of at least 80% of the expected number of doses of study product over the two weeks of product use.
- The proportion of participants who at their Two-Week Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during sexual intercourse in the future.
- Reported positive and negative aspects of using study product
- Changes in vaginal flora

Exploratory Objectives

- Determine the pattern of cytokine/chemokine, innate immune factor changes, and functional activity associated with use of VivaGel[®] in the lower reproductive tract of healthy sexually active HIV-negative women aged 18-24 years.
- Determine the extent of SPL7013 absorption into the blood following the completion of product dosing
- To assess the effects of VivaGel[®] on colposcopic findings

Exploratory Endpoints

- Changes in cervical cytokine, innate immune factor (secretory leukocyte protease inhibitor (SLPI) and lactoferrin) expression, and functional activity (antiviral and antibacterial) in cervicovaginal secretions
- Detection of SPL7013 in blood samples at Day 0 and Two-Week Clinic Visit (Target Day 14)
- Assessment of colposcopic findings

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel[®]) Applied Vaginally in Sexually Active Young Women

MTN Protocol Number: MTN-004

Co-Sponsor Number: SPL7013-006

Date: 30 June 2008

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St. Petersburg, FL 33701

Site Laboratory: Tampa General Hospital
2 Columbia Drive
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Tampa, FL 33606

Site Laboratory: University of Puerto Rico
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1.6 Data Center

Data Center: Statistical Center for HIV/AIDS Research & Prevention
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N., LE-400
PO Box 19024
Seattle, WA 98109-1024

1.7 Study Operations

Study Operations: Family Health International (FHI)
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2 INTRODUCTION

2.1 HIV/AIDS Prevention and Microbicides

According to UNAIDS, an estimated 33.2 million (30.6 million–36.1 million) people worldwide were living with human immunodeficiency virus (HIV) in 2007. An estimated 2.5 million (1.8 million–4.1 million) became newly infected with HIV and an estimated 2.1 million (1.9 million–2.4 million) lost their lives to acquired immunodeficiency syndrome (AIDS)(1). Given these statistics, it is clear that available prevention options today have been insufficient to stem the tide of the AIDS epidemic, particularly for women, who continue to comprise a growing proportion of new HIV infections around the world. There is an urgent need for prevention methods that women can initiate and control themselves. Topical microbicides represent one such method, and a growing body of data suggests that a safe and effective topical microbicide will be a real option for women in the future. Many candidate microbicides are currently in various stages of preclinical and clinical investigation; VivaGel[®] is a dendrimer-based topical microbicide candidate with significant promise as a safe and effective means of prevention of HIV transmission.

2.2 The MTN Research Agenda

The MTN microbicide development plan has been designed to move candidate microbicides such as VivaGel[®] from the preclinical evaluation phase through to licensure. Candidate microbicides are considered for MTN development if they meet the following minimum criteria; (i) the International Working Group on Microbicides (IWGM) criteria for advancement into Phase 1 human studies, (ii) the commercial sponsor must be able to provide sufficient quantities of the candidate to undertake Phase 1 studies, (iii) the sponsor must have a formulation appropriate for human administration or be prepared to subcontract formulation development to agencies such as the NIAID/DAIDS formulation subcontract, (iv) the IND should have been submitted, and (v) an updated Investigator's Brochure must be available. VivaGel[®] is a product that meets all of these criteria.

2.3 Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN)

The MTN will collaborate with the ATN to carry out MTN-004. The ATN has been the only national network focused on studying the emerging HIV epidemic in teens infected through sex or drug-injecting behaviors. The scientific findings generated within this network inform the nation's adolescent-specific HIV/AIDS scientific agenda to improve HIV prevention efforts and the medical and psychosocial management of HIV-infected teens. The National Institute of Child Health and Human Development (NICHD) supports the ATN and its infrastructure with the capacity for behavioral, microbicial, prophylactic, therapeutic, and vaccine trials to take full advantage of results gleaned from detailed observational and laboratory-intensive studies.

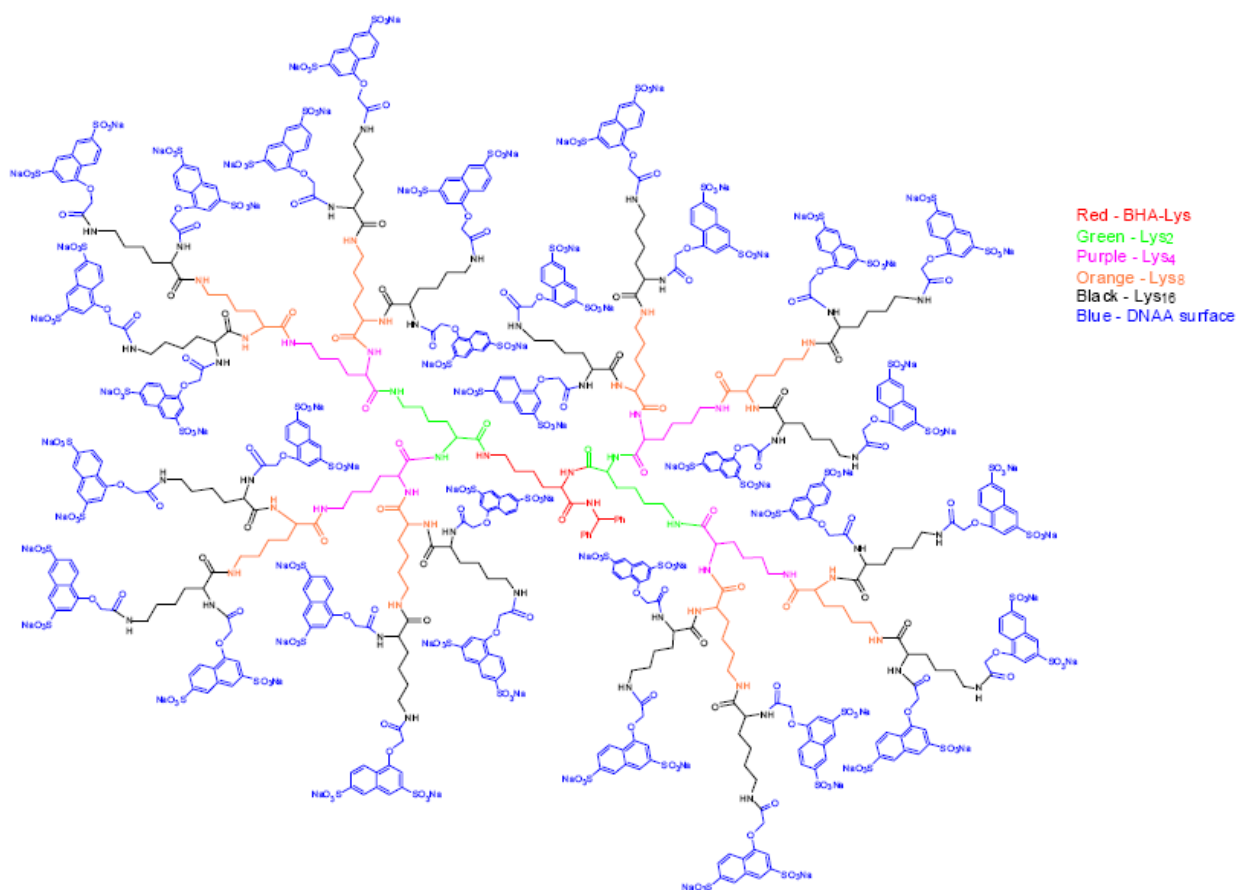
The primary mission of the ATN is to conduct research, both independently and in collaboration with existing research networks on promising behavioral, microbicial, prophylactic, therapeutic, and vaccine modalities in HIV-infected and HIV-at-risk adolescents, ages 12 through 24 years. The ATN brings expertise and resources to collaborative protocol development that ensures feasible and acceptable study design as well as experience in recruiting and retaining this unique population. For the purposes of collaborative research, the resources in the ATN support the site-specific and negotiated participant-specific costs entailed in collaborative research activities, and do not duplicate but draw upon the regulatory, drug repository, laboratory, forms design, database management, and statistical capacity available in the NIH-funded research networks which choose to collaborate with the ATN.

2.4 SPL7013

SPL7013 is the active pharmaceutical ingredient (API) which, when formulated into a vaginal gel, is known as SPL7013 Gel or VivaGel[®]. Dendrimers are a relatively new class of macromolecules characterized by multiple layers of subunits branching out from a central core; they are constructed by repeated stepwise addition of branching units to a core(2). During lead optimization for dendrimer-based microbicides with HIV and herpes simplex virus (HSV) antiviral potential by Starpharma Pty Ltd, SPL7013 emerged as a candidate with significant antiviral properties. In addition it was the easiest to prepare on large scale as a single molecular species, having the optimal formulation compatibility and an excellent stability profile. Under IND 62,482, VivaGel[®] was granted “Fast Track” status by the U.S. Food and Drug Administration (FDA) for the HIV prevention indication. Further information on the formulation of VivaGel[®] is noted in Section 6. A sufficient body of preclinical and clinical safety data exists to support further clinical testing of VivaGel[®]. This section summarizes *in vitro*, animal, and clinical studies to date. Further detailed information is available in the SPL7013 Gel (VivaGel[®]) Investigator’s Brochure(3).

The chemical name for SPL7013 is 2,6-bis-((1-naphthalenyl-3,6-disulfonic acid)-oxyacetamido)-2,6-bis-2,6-bis-2,6-bis-(2,6-diamino-hexanoylamino)-2,6-diamino-hexanoic acid (diphenylmethyl)-amide, polysodium salt. The underlying dendrimer architecture of SPL7013 is created by the addition of (L)-lysine molecules in layers or generations radiating out from a divalent core (the benzhydrylamine amide of (L)-lysine). The last step in the synthesis of SPL7013 involves attachment of 32 copies of a naphthalene-3, 6-disulfonate derivative to form the outer surface. The completed structure is an example of a polylysine dendrimer and the molecular weight is 16,582 Da). The structure of SPL7013 is noted in Figure 1.

Figure 1. Chemical structure of SPL7013



SPL7013 is a member of the class of compounds called dendrimers, a chemically diverse array of macromolecules. As pharmaceuticals, dendrimers offer a unique single-molecule structure for the presentation of multiple copies of a given surface group which are attached to the underlying dendrimer architecture through linkers(4). VivaGel[®] is a water-based Carbopol[®] gel buffered to a physiologically compatible pH (Table 1: VivaGel[®] Formulation).

Table 1: VivaGel[®] Formulation

Ingredient	Function in Formulation	Amount (weight for weight (w/w))
SPL7013	Antiviral	3.0%
Purified Water, USP	Solvent	qs to 100%
Methylparaben, NF	Antimicrobial preservative	0.18%
Propylparaben, NF	Antimicrobial preservative	0.02%
EDTA	Antioxidant	0.1%
Carbopol [®] 971P	Gelling agent	5.0%
Propylene glycol, USP	Emollient	1.0%
Glycerin, USP	Emollient	1.0%
2N NaOH	pH adjusting agent	qs to pH 5.0

2.4.1 Strength of Active Product

This protocol will utilize the 3% w/w SPL7013 Gel (VivaGel®).

2.4.2 Mechanism of Action

Dendrimers can be synthetically engineered to have properties that prevent virus entry and infection(5). In particular, polyanionic dendrimers are able to block virus attachment to cells or interfere with virus adsorption. SPL7013 is able to interact at multiple target sites, a factor which also enhances its antiviral activity(6).

2.5 Condom Integrity

The effect of VivaGel® on latex condoms has been assessed in a number of studies. VivaGel® did not compromise the integrity of non-lubricated, silicone lubricated, and aqueous lubricated condoms, as assessed by burst pressure, time to burst, burst volume, and tensile strength. The dimensions of the condoms after exposure to the gel also appeared to be unchanged.

2.6 Anti-HSV Activity

In vitro and *in vivo* studies in mice on a selection of dendrimer-based compounds have reported potent inhibition of HSV-1 and HSV-2(7). In a mouse model, unformulated SPL7013 provided significant protection from genital herpes disease and infection at concentrations as low as 1 mg/mL and for at least 1 hour following topical (vaginal) administration of 10 mg/mL(6). SPL7013 formulated into VivaGel® and two related formulations was further evaluated in mouse and guinea pig models of genital herpes infection. In the murine evaluations each of the formulations provided significant protection at concentrations of 10 and 50 mg/mL. Formulated SPL7013 provided protection for at least 1 hour at a concentration of 10 mg/mL. The VivaGel® formulation was chosen for dose ranging experiments using the guinea pig model of vaginal genital herpes. The guinea pig evaluations suggested that doses of 30 to 50 mg/mL were required for optimal protection. The results of these evaluations indicate that SPL7013 shows significant promise as a microbicidal product with antiviral activity.

2.7 Anti-HIV-1 Activity

In vitro studies of SPL7013 have demonstrated antiviral activity against HIV type 1 (IC₅₀=1.90 µg/mL), HIV type 2 (IC₅₀=4.38 µg/mL) and chimeric-simian human immunodeficiency viruses (SHIV) (IC₅₀=0.25 µg/mL). The antiviral properties of polyanionic dendrimers are mediated by multiple mechanisms including inhibition of viral transmission, attachment, fusion, and replication.

Studies of inhibition of attachment, fusion, and viral replication found no significant cytotoxic effects of SPL7013 at concentrations up to 100 µg/mL (highest concentration tested). The cellular cytotoxicity of SPL7013 in human PBMCs was reassessed against

two previously tested strains (one type of HIV-1 Clade D and one type of HIV-1 Clade O); this study confirmed SPL7013 efficacy against these strains, with therapeutic indices of >676 and >1348 against Clade D and O, respectively.

Cervical and colorectal explant cultures were exposed to HIV-1 in the presence or absence of 5% SPL7013. In the absence of SPL7013, the cervical and colorectal explant cultures replicated HIV-1, which peaked approximately by day 14 of culture. SPL7013 blocked infection in 3 of 4 colorectal explant cultures and in 2 of 2 cervical explant cultures. This was significant inhibition of HIV-1 infection in these tissues.

A SHIV-challenge study of female pigtailed macaques (8 animals/untreated, 8 animals/placebo, 6 animals/active treatment group, up to 5% w/w SPL7013 Gel, single dose) found that 3-5% w/w SPL7013 Gels were effective in blocking vaginal transmission of a single virus challenge with SHIV(8). Neither SPL7013 nor placebo gel produced any adverse effects following the single application.

Table 2: Effects of SPL7013 Gels on Vaginal Transmission of SHIV_{89.6P} in Macaques

Treatment Group	Number of Animals	Virus Isolation*	Viral DNA PCR*	Plasma Viral RNA*	CD4 Cell Depletion*	Anti-SHIV Antibody*	% Infection
5% w/w SPL7013 Gel	6	0	0	0	0	0	0
3% w/w SPL7013 Gel	6	1	1	1	1	1	16.7
1% w/w SPL7013 Gel	6	4	4	4	4	2	66.7
Placebo Gel	8	7	7	7	7	5	87.5
Untreated control	8	8	8	8	8	6	100

*Results of each assay expressed as number of positive macaque(s) per total tested.

2.8 *In vitro* Studies

2.8.1 Cytotoxicity

In vitro studies of cytotoxicity suggest that SPL7013 has a significant therapeutic index, with little potential for cytotoxicity. An investigation of SPL7013 5% formulation in colorectal and urogenital epithelial cell lines and primary immune cells found the microbicide to be relatively non-toxic as determined by an ATP-dependent luminescence assay. SPL7013 did not affect an intact, polarized epithelial monolayer, a potential marker for product safety on mucosal epithelia(9).

Human cervical explant cultures were used to evaluate potential toxicity of SPL7013 Gel. Histological analysis of cervical tissues exposed to 5% w/w SPL7013 Gel and placebo showed regenerated epithelium and an intact lamina propria similar to the untreated control. Further, an MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay confirmed these results(10). A recent study utilized a human colorectal

explant culture to evaluate the potential toxicity of SPL7013 Gel, among others(11). This model found shedding of epithelium with intact lamina propria to occur in association with exposure to 5% SPL7013, without evidence of necrosis on histological analysis. An MTT assay confirmed these results. Viability of tissues treated with SPL7013 was not significantly different from that of the control media. Spermatozoa Motility SPL7013 was not shown to be spermicidal in a modified Sander-Cramer assay. Motile spermatozoa were noted following a room temperature incubation of semen with an SPL7013 dilution.

2.8.2 Genetic Toxicity

Based upon negative findings in Ames test and *in vitro* mammalian chromosome aberration assays (Chinese hamster ovary cells), it was concluded that SPL7013 has no mutagenic potential. In an *in vivo* rat micronucleus study, SPL7013 administered intravenously did not increase the incidence of micronucleated polychromatic erythrocytes(12). SPL7013 was negative in this genetic toxicity assay.

2.9 Animal Studies

2.9.1 Oral administration

Multiple toxicity studies performed in rats have suggested a low risk for acute toxicity from SPL7013(12). An oral gavage study of acute toxicity in rats (3 animals/group, 3 groups, up to 1600 mg/kg/day) had no mortality and no clinical signs or effects on animals' body weight were reported. Based on this study, the no-observed-effect-level (NOEL) was estimated to be greater than 1600 mg/kg. Repeated administration of SPL7013 by once daily oral gavage for 14 days was well tolerated in rats at up to 2000 mg/kg/day. Based on the bioanalytical results, there was very limited systemic exposure to SPL7013 after administration of 500, 1000 or 2000 mg/kg/day. There was some evidence that systemic exposure was greater for 2000 mg/kg/day than for the two lower doses, but there was no clear difference between the two lower doses.

Based on these two studies, the no-observed-effect-level (NOEL) was estimated to be greater than 2,000 mg/kg.

2.9.2 Intravenous Administration

A study of intravenous administration of SPL7013 in rats (20 male, 20 female, 5/sex/dosage group, single-dose up to 75 mg/kg) noted signs of toxicity (both clinically and on necropsy) in some animals at the 50 mg/kg and 75 mg/kg dose levels. The NOEL was determined to be 25 mg/kg for the intravenous administration route. A study of intravenous administration in rabbits (2 animals/group, 4 groups, up to 75 mg/kg, single dose) found a dose of 25 mg/kg (the NOEL) well tolerated, but noted adverse effects by clinical and necropsy evaluation in some animals at the 50 and 75 mg/kg dose levels.

In a study of repeated daily intravenous (bolus) injection of SPL7013 for 7 days in rats, SPL7013 was well-tolerated at levels of 0.4 and 1.7 mg/kg/day with only minor, transient clinical signs (decreased activity and reddened ears) noted at 9 mg/kg/day.

2.9.3 Vaginal Administration

Animal studies of vaginal administration of SPL7013 Gel have suggested a low risk for acute toxicity(12). A study of acute toxicity in rats (5 animals/group, 2 groups, placebo vs. 5% gel, 0.1 mL single vaginal dose) found no clinical signs of toxicity or vaginal irritation in either group. No effects were noted in body weight gain. There were no macroscopic changes in systemic organs on necropsy. The NOEL was calculated as 28.6 mg/kg. A study of vaginal administration of SPL7013 Gel in rabbits (3 animals/group, 2 groups, placebo vs. 5% w/w SPL7013 Gel, single dose 1.0 mL test article volume) noted no clinical signs of systemic toxicity in either group, and no effects on body weights, body weight gains, or food consumption. No differences were observed between groups with respect to vaginal irritation following a single vaginal dose.

Studies of repeat-dose toxicity in rats, rabbits, dogs, and macaques also found a lack of evidence for systemic toxicity. A study of rats (10 animals/group, 5 groups, up to 25 mg/kg/day, single daily 0.1 mL dose, 14-day exposure) found minimal vaginal irritation in all dose groups, with no systemic toxicity noted (NOEL >25 mg/kg). Rabbits receiving vaginal SPL7013 Gel (5 animals/group, 5 groups, up to 5% w/w SPL7013 Gel, single daily 1.0 mL dose, 14-day exposure) were not observed to have significant vaginal irritation or signs of systemic toxicity (NOEL >12.5 mg/kg). Dogs receiving vaginal SPL7013 Gel (2 animals/group, 4 groups, up to 5% w/w SPL7013 Gel, single daily 1.0 mL dose, 14-day exposure) were not observed to have significant vaginal irritation or signs of systemic toxicity (NOEL >5% w/w SPL7013 Gel). A dose-related increase in the severity of subacute inflammation was noted in the cervix and vagina (proximal, mid, and distal sections) of the dogs. This occurred in all animals from all groups, including the vehicle control.

Chronic toxicology studies have been conducted in which mice (90 days), rats (6 months) and dogs (9 months) received daily vaginal doses with placebo, 1, 3, or 5%w/w SPL7013 Gels(12). Additional data were obtained by conducting interim sacrifices after 90-days in both rat and dog chronic studies. In all three species, no evidence of systemic toxicity was observed. In addition, no detectable levels of SPL7013 have been measured in the plasma. Minor microscopic changes were noted such as a dose-related increase in the incidence and severity of glandular dilatation of the cervix and uterus, and dose-related vaginal changes (distal, mid, and proximal portions) that included minimal to mild epithelial cell hyperplasia and minimal single cell necrosis in mice, minimal to mild epithelial hyperplasia, minimal cervical vacuolation and minimal to mild luminal exudate in the vagina in rats, and test article-related microscopic observations limited to the cervix and vagina in dogs, including vacuolated macrophages in the submucosa and subacute inflammation. The pattern of microscopic findings (in terms of number and degree of severity) was the same at the

termination of each study (6 months in rats, or 9 months in dogs) as that noted at the 90 day interim sacrifice. In all studies, the sub-chronic inflammation observed microscopically did not escalate to show any signs of chronic inflammation or a more pronounced immune response. In the mice and rats, the NOEL was determined to be 5%w/w SPL7013 Gel, while in dogs it was 3%w/w SPL7013 Gel.

A study in pigtailed macaques (6 animals/group, 3 groups, receiving 0%, 1%, 3% and 5% w/w SPL7013 Gel in a 1.5 mL volume, four consecutive daily applications) examined the vaginal safety of SPL7013(13). Vaginal safety measures included colposcopy, vaginal pH, and microflora determinations. Cervicovaginal tissue disruption and/or friability were noted in four of six animals receiving the 5% w/w SPL7013 formulation. None of the animals treated with the 1% or 3% w/w SPL7013 Gel formulation demonstrated cervicovaginal irritation. Observations of subepithelial vasculature were noted in the majority of animals from each arm of the study. Statistically significant decreases in vaginal pH were noted 30 minutes after the application of each SPL7013 Gel formulation, and remained lower than baseline at 24 hours after application. These values were recovered to baseline at the Day 8 measurement. Differences in vaginal pH were not statistically significant in comparison to values noted after application of placebo gel (base formulation without added SPL7013) at these time points.

In the same macaque study, when quantities of vaginal microflora between placebo and treatment groups were compared, there were few significant differences. Of the daily comparisons, significant differences were found between the placebo-treated group and the 3% w/w SPL7013 Gel treated group concerning H₂O₂-producing lactobacillus on day 4 and between the placebo-treated group and the 5% w/w SPL7013 Gel treated group concerning H₂O₂-producing lactobacilli on day 5. No significant differences were noted on the other study days. Due to the small sample size, the investigators did not conclude that these were true differences, and no pattern of product-induced suppression of these organisms emerged.

Profiles of vaginal and cervical biopsy specimens collected from macaques in the same study 24 hours after the final application of 1%, 3%, and 5% w/w SPL7013 Gel were mostly similar to baseline profiles assessed in these studies (layers of epithelial cells, presence of polymorphonuclear cells, plasma cells and lymphocytes). Biopsy specimens from animals that received the test gel had histologic profiles similar to those that received placebo. Although statistical analyses indicate an increase in presence of plasma cells in the 1% SPL7013 treated animals, these increases reflected no more than one cell greater than the normal profile range (0-4 cells per high power field). No clinical significance was attached to these findings (unpublished data). Overall, repeated daily vaginal use of 1% and 3% w/w SPL7013 Gels resulted in an acceptable safety profile, as evaluated by colposcopy, pH determination, microflora evaluation, and histology, compared to the profiles achieved with the placebo gel.

Taken together, repeated vaginal administration of SPL7013 Gels (0% to 5%) to multiple species generally produced a low grade response. There was no clear indication from any of the studies of a potential safety concern for humans.

2.9.4 Penile Administration

A study of penile administration in dogs (3 animals/group, 2 groups, placebo vs. 3% w/w SPL7013 Gel) found the test article to be well tolerated, with no effects noted on clinical observations, including degree of erythema, edema, body weights, or food consumption (NOEL >3.4 mg/kg).

2.9.5 Rectal Administration

A study of rectal administration in macaques (8 animals, crossover design, 3% w/w SPL7013 Gel vs. placebo vs. no product, 3 daily applications of single dose 2.5 mL gel or no product) found 3% w/w SPL7013 Gel to be well tolerated by rectal tissues and microflora compared to tolerance of the placebo gel(13).

2.9.6 Developmental Toxicology

A study of vaginal administration in rats (25 animals/group, 4 groups, up to 5% w/w SPL7013 Gel, 0.1 mL daily dose for 12 days) found no evidence of teratogenicity at any dose (NOEL >25 mg/kg or 5% w/w SPL7013 Gel). A study of vaginal administration in rabbits (23 animals/group, 4 groups, up to 5% w/w SPL7013 Gel, 1.0 mL daily dose for 14 days) did not find evidence of developmental toxicity. This study reported maternal deaths, but based on follow-up studies and histopathological evaluation, these mortalities were concluded to be the result of a local, facility/procedure related and species-specific response that has an understood pathogenesis. Further details are available in the Investigator's Brochure.

2.9.7 Pharmacokinetics

SPL7013 was not detected in plasma samples drawn from those animals that were dosed vaginally with SPL7013 Gel in the mouse, rat, rabbit and dog repeat dose studies and rabbit teratology study that are described above. The identified lower limit of quantification (LLOQ) of SPL7013 in these plasma samples was 0.2 to 0.5 µg/mL (12 to 30 nM).

2.9.8 Contraceptive Activity

The effect of 3% w/w SPL7013 Gel, or 3% w/w of the active ingredient, SPL7013, in hydroxyethylcellulose (HEC) gel, on contraception in female New Zealand White rabbits has been studied. Animals were artificially inseminated with 0.5 mL of sperm 5 minutes after vaginal administration of 2mL of the gels containing SPL7013. HEC gel was used as a placebo control. Contraceptive efficacy was determined 15 days post insemination

by assessing whether or not the animal became pregnant, and by comparing the number of implanted embryos in pregnant animals.

Out of 8 rabbits pre-treated with 3% w/w SPL7013 Gel, only 2 became pregnant, with 6 and 7 embryos counted in each of the pregnant does. Out of 8 rabbits pre-treated with 3% w/w SPL7013 in HEC Gel, again only 2 became pregnant. There was only one embryo in each of the pregnant does. In contrast, 9 of 11 rabbits in the HEC placebo control group became pregnant with a total of 75 embryos. Preliminary observations were also made to determine the duration of contraceptive effect. The combined results demonstrated that 3% w/w SPL7013 Gel was a highly effective contraceptive approximately 24 hours after application. The results also suggest that contraceptive efficacy diminished 2 days after application, and was no longer present at 7 days.

2.10 Clinical Studies

Clinical experience so far with SPL7013 Gel is comprised of three completed Phase 1, randomized, placebo-controlled studies(12). The first study investigated the safety and tolerability of a 3.5g dose of different strengths of SPL7013 Gel (0.5%, 1% and 3%w/w SPL7013) when administered once daily into the vagina of healthy, sexually inactive, female volunteers (Study No. SPL7013-001)(12). The second study investigated the safety and tolerability of 2g of 3%w/w SPL7013 Gel when administered once daily to the penile epithelium of healthy male volunteers (Study No. SPL7013-002)(12). The third study investigated the safety and tolerability of 3.5g of 3%w/w SPL7013 Gel when administered vaginally, twice daily for 14 days in healthy, sexually inactive, female volunteers (Study No. SPL7013-004)(12). Data from the three completed safety studies indicate that 3% SPL7013 Gel is safe and well tolerated when administered to the vaginal epithelium once or twice daily for up to 14 consecutive days in sexually abstinent women, and to the penile epithelium once daily for seven consecutive days.

Study No. SPL7013-001: Participants consisted of 37 healthy females aged between 18 and 43 years, all with regular menstrual cycles(12). A total of 36 participants completed all components of the trial, with one volunteer withdrawn due to a finding present prior to dosing that was deemed unrelated to study procedures or study product.

Table 3: Design of First Clinical Study in Women

Group	N	Dose Level	Doses	Interval
1	12 (8 active, 4 placebo)	0.5% w/w SPL7013 Gel	7	24-hour
2	12 (8 active, 4 placebo)	1.0% w/w SPL7013 Gel	7	24-hour
3	13 (9 active, 4 placebo)	3.0% w/w SPL7013 Gel	7 for 12 participants, 3 for 1 participant	24-hour

Safety evaluations included clinical symptom assessment, vital sign measurements, clinical laboratory diagnostic results, colposcopic examination of the vulva, vagina, and cervix, and examination of the vaginal microflora. No serious adverse events (SAEs) were reported in this trial. Adverse events (AEs) were experienced by 31 of 37

participants, with a total of 13 events having a possible causal relationship to study treatment (active or placebo). All reported AEs were deemed to be of mild or moderate intensity except for a tension headache of severe intensity reported by a participant who received the placebo gel, but this event was not considered to be related to study treatment. Of the moderate intensity AEs, the only one judged possibly related to study treatment was a rash on the jaw-line, experienced by a participant receiving placebo gel. All other AEs, which were possibly related to study treatment, were of mild intensity.

Table 4: Reported AEs Possibly Related to Study Treatment

AE	Participants Receiving Active	Participants Receiving Placebo
Mild abdominal pain	4	1
Mild dysuria	1	0
Mild genital pruritus	0	1

Common AEs judged unlikely to be or not related to study treatment included headache, metrorrhagia, and venipuncture site bruise. No identifiable trends in AEs were observed when analyzed by type or by dose of study agent. On colposcopy, no participants showed signs of vulvar, vaginal or cervical inflammation or other pathology related to gel exposure. Analysis of vaginal flora in both active and placebo groups noted lower concentrations of normal lactobacilli, higher concentration of facultative gram-negative rods, and a decrease in proportion of anaerobic forms. This change in flora was not associated with any cases of vaginal infection, and flora generally returned to pre-gel levels by the Day 14 follow-up visit. Most participants experienced leakage of the gel across all SPL7013 Gel treatment groups (24 out of 25) on at least one occasion during the dosing period, but the volume of discharge was small, and was transitory. The discharge in all instances was not associated with vaginal burning, pruritus or malodor, and was easily tolerated. No clinically relevant changes in vital sign measurements or laboratory values were noted. SPL7013 plasma concentrations were measured by a validated, bioanalytical capillary electrophoresis method in all participants who received the highest dose level (3.0% w/w SPL7013 Gel). No SPL7013 was detected in any plasma sample analyzed during the study (LLOQ = 0.5 µg/mL [30nm]).

Study No. SPL7013-002: A total of 37 healthy male subjects aged 18 years or older were enrolled in the study and a total of 36 subjects completed all aspects of the study(12).

The genital adverse events reported throughout the study were mild (grade 1) and benign in nature and most lasted for less than 24 hours. A total of 12 genital AEs were reported by 33% of study participants in the 3% SPL7013 Gel group (8 of 24 men), compared with 5 genital AEs reported by 33% of study participants in the placebo group (4 of 12 men). There was no difference in the incidence of genital events between the SPL7013 Gel and placebo groups when analyzed either for all genital AEs or for those genital AEs deemed to have a potential causal relationship with study product. The most commonly reported events were genital pruritus (penile itch) (12% participants in SPL7013 Gel group and 8% in placebo) and application site erythema (penile redness) (4% in SPL7013 Gel group and 25% in placebo). No patterns emerged in genital

events between the circumcised and uncircumcised strata in either SPL7013 Gel or placebo treatment groups.

There were no SAEs in any of the subjects during this study, nor any grade 3 or 4 AEs. There was no evidence of systemic toxicity in either treatment group. Of the 32 non-genital AEs reported, 16 were deemed to have a potential causal relationship to study product (6 AEs were reported by 25% participants in the SPL7013 Gel group, and 10 AEs were reported by 33% participants in the placebo group). Three non-genital AEs were considered potentially related to study product and reported as moderate in intensity (grade 2), however all were reported by participants in the placebo treatment group. All other nongenital AEs deemed to be possibly related to study treatment were of mild intensity. The most commonly reported AE was headache with 13% participants reporting in the active group compared with 25% participants in the placebo group. All other non-genital AEs were reported in no more than one participant in each treatment group.

As with the study in females, no discernible trends in AEs were observed in this study, and no SPL7013 was detected in any plasma sample analyzed during the study.

Study No. SPL7013-004: A total of 54 healthy women were enrolled in the study with 35 receiving SPL7013 Gel and 19 receiving placebo(12).

There were no grade 3 or 4 AEs, and no deaths or SAEs reported during the study. The proportion of participants that experienced an AE during the study was not statistically different between the SPL7013 and placebo arms. The most common AEs included vaginal discharge, laboratory abnormalities, metrorrhagia, abdominal symptoms, candidiasis, headache, and vaginal and vulvar pain.

Maintenance of normal vaginal flora, in particular H₂O₂-producing lactobacilli, was common in women throughout the dosing period and overall study, and did not differ by study arm. No laboratory abnormalities were deemed to be clinically significant; these were balanced between the SPL7013 Gel and placebo arms, and none were grade 3 or higher.

There were no study participants that discontinued product use due to any AE indicating that SPL7013 Gel and the placebo were well tolerated.

In keeping with other clinical and non-clinical studies of SPL7013 Gel, no SPL7013 was detected in plasma samples collected during the study.

2.11 VivaGel[®] Placebo

The VivaGel[®] placebo for this study is the base formulation without SPL7013. The placebo gel to be used in this study is formulated primarily from water, but also contains Carbopol[®] and other ingredients as outlined in Section 6.2. Carbopol[®] is one of the most widely used excipients for thickening topical lotions, creams and gels. Carbopol[®]

and other types of similar polymers are also used to modify the rheology (flow properties) of water-based systems and to stabilize multi-phase systems such as emulsions and suspensions(14). Also known as carbomer, this type of thickener is a high-molecular weight polymer that is not absorbed by body tissues.

Table 5: VivaGel® Placebo Formulation

Ingredient	Function in Formulation	Amount (w/w)
Purified Water, USP	Solvent	qs to 100%
Methylparaben, NF	Antimicrobial preservative	0.18%
Propylparaben, NF	Antimicrobial preservative	0.02%
EDTA	Antioxidant	0.1%
Carbopol® 971P	Gelling agent	5.0%
Propylene glycol, USP	Emollient	1.0%
Glycerin, USP	Emollient	1.0%
2N NaOH	pH adjusting agent	qs to pH 5.0

2.11.1 *In vitro* Studies

Carbopol®, the gelling agent in the placebo gel, has been the subject of numerous *in vitro* studies. Biological oxygen demand tests have demonstrated that the biological oxygen demand of Carbopol® crosslinked polyacrylic acid polymers is zero, contributing to an excellent shelf life in severe environments(15). The Carbopol®-based aqueous placebo gel planned for use in this study was found to be not disruptive to transepithelial resistance at a nontoxic product concentration. Using a cervical explant culture model, a Carbopol®-containing placebo did not affect tissue viability as compared to the control based on the MTT assay(16). Further, tissue architecture appeared histologically normal. A subsequent study utilizing a human colorectal explant culture model found explants treated with this placebo gel to be histologically normal. Results from an MTT assay showed a non-significant reduction in viability of intestinal explants exposed to SPL7013 compared to those exposed to the medium control.

2.11.2 Animal Studies

Carbomer is the generic name adopted by United States Pharmacopeia (USP) for various Carbopol® homopolymers. Acute oral studies with rats, guinea pigs, mice and dogs showed that carbomers have low toxicities when ingested. No mortalities occurred in rabbits injected intravenously with 1%, 2% or 3% carbomer in aqueous solution at a dose of 5 mL/kg. Rabbits showed minimal skin irritation when tested with 100% carbomer, and zero to moderate eye irritation when tested with carbomers and/or their various salts at concentrations of 0.20-100%(17).

Single and repeated dose oral, intravenous and vaginal administration in rats and rabbits of the base placebo gel (base formulation without added SPL7013) planned for this protocol was not associated with significant adverse clinical effects or systemic toxicity. Repeat dose penile administration in dogs of this placebo gel was also well tolerated and not associated with adverse clinical effects or systemic toxicity.

A study in pigtailed macaques (6 animals/group, 3 groups, placebo, 1 and 5% w/w SPL7013 Gel, followed by a separate assessment of the 3% w/w SPL7013 Gel controlled by a repeat of the placebo arm) examined the vaginal safety of SPL7013 and the base placebo gel [12]. Mild erythema was noted in 2 of 12 placebo-treated animals. There were no statistically significant differences in pre- and post-application pHs with the placebo gel in this study. Rectal administration of the placebo gel in pigtailed macaques was associated with a slightly increased level of epithelial desquamation(13).

2.11.3 Clinical Studies

Powdered Carbopol[®] polymers have a long history of safe use in cosmetic and pharmaceutical products(15). Clinical studies with carbomer and its various salts showed that these polymers have low potential for skin irritation and sensitization at concentrations up to 100%. Propylene glycol and glycerin (other ingredients in the placebo gel formulation) are both generally recognized as safe (GRAS) for use in humans. Methylparaben and propylparaben are affirmed GRAS Direct Food Substances in the USA at levels up to 0.1%, and are widely used in vaginal formulations at levels of 0.1-0.18% and 0.02-0.1%, respectively.

MTN-004 will utilize as the placebo gel the same Carbopol[®]-based aqueous gel that was utilized in clinical protocol number SPL7013-001, SPL7013-002, and SPL7013-004(12). As previously mentioned, these studies had no deaths or SAEs. In study SPL7013-001, AEs that were considered to be possibly related to the study treatment were experienced by 3 of 12 participants receiving placebo, including one moderate AE (rash on jaw-line). The only AE reported of severe intensity was a tension headache in a placebo recipient, although this was not deemed related to study product or procedures. Eleven participants who received placebo gel reported product leakage on one or more occasions, but without complaints of burning, itching or unpleasant odor. One participant who received placebo gel reported itching without associated discharge. No participants receiving placebo gel had colposcopic findings consistent with inflammation or other pathology related to study agents. Lower concentrations of vaginal lactobacilli with a concomitant increase in colonization with facultative gram-negative rods were noted on vaginal culture during placebo gel use, but no cases of bacterial vaginosis or any intermediate Nugent score were identified. No clinically relevant changes were noted in vital signs or clinical laboratory diagnostic results.

In study SPL7013-002, 5 genital AEs were reported by 33% of study participants in the placebo group (4 of 12 men)(12). The most commonly reported events were genital pruritus (penile itch) (8% participants in placebo) and application site erythema (penile redness) (25% in placebo). Three non-genital AEs were considered potentially related to study product and reported as moderate in intensity (grade 2), however all were reported by participants in the placebo treatment group. The most commonly reported AE was headache with 25% participants reporting in the placebo group.

In study SPL7013-004, signs and symptoms of localised genital irritation potentially associated with administration of the study product were experienced by 47% of

participants in the placebo arm. There were no effects of placebo gel on vaginal flora or laboratory parameters in this study.

2.12 HEC Gel

HEC gel or the “universal” placebo gel is a vaginal product which contains hydroxyethylcellulose as the gel thickener, purified water, sodium chloride, sorbic acid and sodium hydroxide(18). The gel is isotonic and formulated at a pH of 4.4 to avoid disrupting the normal vaginal pH and has minimal buffering capacity in order to avoid the inactivation of sexually transmitted pathogens. Hydroxyethylcellulose, the gelling agent, is used to approximate the viscosity of other microbicide gel candidates. Each pre-filled applicator will deliver approximately 4 mL of placebo gel. Placebo gel should be stored at 25°C. Excursions are permitted between 15°C and 30°C.

Table 6: HEC Gel Formulation

Ingredient	Function in formulation	Amount (w/w)
Purified Water, USP	Solvent	96.3
Hydroxyethylcellulose, NF	Gelling agent	2.7
Sodium Chloride, USP		0.85
Sorbic Acid, NF	Preservative	0.1
Sodium Hydroxide, NF	pH adjusting agent	qs pH 4.4

2.12.1. Strength

There is no active ingredient in the HEC gel. 2.7% w/w HEC gel will be used in this study.

2.13 Anti-HSV Activity

CF-1 mice (n=10 per group) pretreated with medroxyprogesterone acetate were administered 0.02 mL of HEC gel or phosphate-buffered saline (PBS) vaginally, followed by a 0.01 mL of HSV-2 viral inoculum of 10 ID₅₀ 0.3 minutes later. On day 3, vaginal lavage was cultured on human foreskin fibroblasts, and mice were considered infected if a cytopathic effect was observed after 3 days of incubation. Infection rate following pretreatment with HEC gel (90%) was not significantly different from pretreatment with PBS (80%) or from mice given no treatment (80%). HEC gel did not enhance susceptibility of mice to HSV-2 when administered 12 hours before vaginal challenge.

2.14 Anti-HIV-1 Activity

In vitro analyses of anti-HIV activity were also performed on HEC gel following a viral binding assay that consisted of a 2-hour incubation of test compound, HIV-1_{IIIB}, and MT-2 cells(18). Cell culture followed by further assessments performed after this incubation period showed no significant antiviral or cytotoxic activity. The HEC gel had negligible effect on virus-induced cytopathic effect at a 1:5 dilution, the highest concentration

tested(19). Additional *in vitro* studies on potential HIV-1 infection of neoplastic T cell lines concluded that the HEC gel had little or no effect on the infection and replication of HIV in human target cells, or the specific replication steps of virus attachment or cell-to-cell fusion(18).

The effect of the HEC gel on vaginal transmission of SHIV_{162p3} (10^3 TCID₅₀) to rhesus monkeys (n=5, n=3, respectively) was determined in two separate studies(19). Macaques pretreated with medroxyprogesterone acetate were vaginally administered 1 mL of the HEC gel formulation 15 minutes prior to challenge with 0.5 mL SHIV_{162p3}. Investigators monitored total RNA load in the animal plasma for a total of 8 weeks by means of a standard quantitative RT-PCR. The first study utilized the HEC gel formulation at pH 6.5; the second study utilized a formulation at pH 4.4. In both studies, all monkeys were infected, as determined by the presence of viral RNA in circulating blood, regardless of the pH of the formulation.

2.15 *In Vitro* Studies

2.15.1 Cytotoxicity

Dilutions of the HEC gel in culture medium exhibited negligible toxicity to human vaginal epithelial cells (standard MTT assay), even at the lowest dilution tested (1:2)(18). Exposure of human vaginal epithelial cells to the HEC gel resulted in minimal IL-1 α induction, even at the lowest dilutions tested (lowest dilution, 1:2)(19).

2.15.2 Spermatozoa Motility

Analyses of pH (HEC gel mixed with human seminal plasma, 8.03 ± 0.26) found that the HEC formulation did not show significant buffering capacity and could not acidify the alkaline pH of seminal plasma, a favorable result in a placebo formulation(19). *In vitro* assessments of spermicidal activity utilizing human semen from healthy donors showed that the HEC gel had no significant deleterious effects on sperm motility, even after a 60-minute incubation.

2.16 Animal Studies

2.16.1 I.V. Administration

Up to 55 intravenous injections of HEC were given to dogs (dose and number not specified) without causing injury other than that typical of the other water-soluble cellulose ethers(19). Only transitory changes in the blood picture and the deposition of the material on the intima of the blood vessels were noted. Groups of rats maintained for two years on diets containing HEC (n not specified, up to 5%) did not exhibit any adverse effects(19). HEC has also been administered to rats in single oral doses as high as 23,000 mg/kg without observed toxic effects (n not specified).

2.16.2 Vaginal Administration

A 10-day rabbit vaginal irritation study (10/arm, 2 arms, HEC gel vs. 0.9% saline control) found that the HEC gel was not irritating to the vaginal mucosa of rabbits when dosed daily for 10 days. One animal in the HEC gel group had an instance of vaginal redness (compared to four animals in the saline group), which did not persist and was not evident at the end of the study. Diarrhea, few feces, and soiling of the anogenital area were noted in that animal. Body weight changes were noted to be normal. In 9 of 10 animals, necropsy results were normal. Anogenital soiling was observed in the animal that exhibited erythema during the in-life phase of the study. Histopathologic changes observed were similar to those seen in the control group, and likely attributable to those that occur as a result of the repeated insertion of a catheter, rather than due to any effect of the test samples.

2.16.3 Developmental Toxicology

Intraperitoneal administration of unformulated HEC to pregnant mice in a 1% and 4% concentration caused an increase in resorptions, but no detectable increase in birth defects(20). While no epidemiological studies of congenital anomalies in infants born to women exposed to HEC during pregnancy have been reported, the Teratogen Information System (TERIS) considers the magnitude of teratogenic risk to a child born after exposure during gestation to be none(21).

2.16.4 Pharmacokinetics

When swallowed, the cellulose ethers, such as HEC, are not absorbed to any appreciable degree and appear unchanged in the feces.

2.17 Clinical Studies

Unformulated HEC is known to be a non-irritating substance in humans (skin sensitization is unusual), with doses less than 2 gm/kg by ingestion not expected to be toxic(21). No inhalation studies have been conducted, but exposure of humans to the dust in manufacturing operations over many years has not led to any known adverse effects. The HEC gel formulation was developed and adopted for use in the HPTN 035 microbicide study, the Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides Buffer Gel and 0.5% PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women.

A randomized, closed label, Phase I study of daily vaginal HEC gel exposure was conducted in 2003(22). In this trial, 30 women were randomized to twice-daily vaginal applications of 3.5 mL of HEC gel or polystyrene sulfonate (PSS) vehicle. The primary objective of this study was to assess and compare the effects of the test articles on symptoms and signs of irritation of the external genitalia, cervix, and vagina as seen on naked eye exam after 7 and 14 days of use including disruption of the epithelium and blood vessels as seen on colposcopy after 14 days of use. Secondary objectives

included: an assessment and comparison of differences in vaginal health by evaluating the results of wet mounts, pH, and Gram-stained vaginal smears (Nugent score and neutrophil counts) after 7 and 14 days of use and vaginal cultures after 14 days of use; and an assessment of acceptability of the study products after 14 days of use among participants.

Results of this trial indicated that both gels appear safe for use twice a day for 14 days in sexually abstinent women. Two out of 14 women (14.3%) randomized to the HEC gel reported at least one symptom of mild severity of genital irritation, which included genital burning, soreness and pelvic pain. A lower proportion of women in the HEC group experienced any evidence (signs and/or symptoms) of genital irritation. Three out of 14 women (21.4%) had colposcopic findings that included erythema, petechiae and peeling(23). No deep genital disruption was observed in either product group. Minimal changes in wet mounts, pH, Nugent scores, neutrophils, and vaginal flora were observed in both product groups.

A pilot study to optimize trial procedures for a proposed Microbicides Development Programme placebo controlled trial utilized the universal placebo gel as the study gel. Final analysis of results has not been completed but there were no serious adverse product related events reported(18).

2.18 Study Hypothesis and Rationale

2.18.1 Study Hypothesis

MTN-004 hypothesizes that VivaGel[®] will be safe, well-tolerated and acceptable for twice daily vaginal application among healthy sexually active young women.

2.18.2 Rationale for Sexually Active Study Population

This will be the first study of VivaGel[®] in a sexually active study population. Studies of safety and acceptability in a sexually active population of women are important for understanding the potential of a candidate microbicide for several reasons. A vaginal microbicide, if approved, is intended for use by sexually active women, and thus must be evaluated for acceptability by this population. In addition, the product should have its safety profile evaluated in women who are experiencing the mechanical effects of intercourse on vaginal and cervical epithelial integrity.

Based upon protocol stipulations and preclinical investigations of the study product to date, neither VivaGel[®] nor either type of placebo gel is expected to be associated with adverse effects or toxicity in male partners of female study participants. Female volunteers will be informed at the Screening Visit and then reminded at all subsequent study visits that male partner knowledge of study participation is encouraged and left to the volunteers' discretion, and that male condom use is a protocol-specified requirement for study participation. According to the results of male condom integrity studies, VivaGel[®] does not compromise the integrity of latex male condoms, as assessed by

burst pressure, time to burst and burst volume, with no apparent change in dimension of male condoms after exposure to the gel. Volunteers who are unwilling or unable to comply with the male condom requirements of this protocol will not be enrolled. Based on a study of penile administration in dogs, no toxicity in male partners is expected in the event of inadvertent exposure. A Phase 1 study of the safety of VivaGel[®] (3% w/w) in male volunteers has indicated that the product was safe and well-tolerated after topical administration to the penis, once a daily for 7 days (Protocol Number SPL7013-002).

In the event that a study participant did not follow protocol guidelines specifying male condom use, it is unlikely that the product would lead to any significant exposure in sexual partners. No quantifiable or significant systemic absorption in female participants is expected. The single completed Phase 1 study of vaginal exposure to VivaGel[®] was conducted in sexually inactive volunteers who remained in a Phase 1 clinical trial unit for the duration of the dosing period, and therefore did not include partner consent. While male partner consent will not be a part of this study, reported instances of unprotected intercourse at any time during the study period will be reported as participant non-adherence to the protocol, as defined by study-specific procedures, with these cases being referred to the physician site investigator for further evaluation according to study-specific procedures if necessary.

2.18.3 Justification of Dosing

The utilization of a 3% w/w SPL7013 dose concentration is based on considerations of safety, potential efficacy, and physical properties of VivaGel[®]. In a study of pig-tailed macaques described above, the safety profile following the use of the 5% SPL7013 formulation did indicate some deleterious effects on the cervicovaginal environment assessed by colposcopy, as compared to the 3% w/w SPL7013 formulation. Investigators evaluating unformulated and formulated dendrimer-based microbicide candidates in mouse and guinea pig models of HSV-2 infection concluded that concentrations of 3% or higher of the formulated SPL7013 product may be necessary for optimal protection against genital herpes. As reviewed above, macaques treated with SPL7013 showed a dose-dependent resistance to SHIV viral challenge, with 3-5% w/w SPL7013 Gels effective in blocking vaginal transmission of SHIV in macaques after single gel application followed by single virus challenge. Studies also indicate that the SPL7013 Gel formulation decreases in viscosity as the concentration of SPL7013 increases. Given these considerations, it seems most scientifically appropriate that clinical research for vaginal application proceed with the 3% w/w SPL7013 Gel formulation.

The dose volume of 3.5 g (equivalent to 3.5 mL) of 3% w/w SPL7013 Gel has been selected as the dose that is intended to provide optimum vaginal and cervical coverage while minimizing leakage of product from the vagina. This balance between coverage and leakage has been investigated using other potential vaginal microbicide candidate gels with similar physicochemical properties to SPL7013 Gel. These studies showed that 3.5 mL of gel provides adequate coverage with minimal leakage(24). 14

consecutive days of dosing is considered to be the maximum length of time in which menses does not overlap with product application and/or follow up visit. Twice daily dosing for 14 days represents the accepted duration of exposure during Phase 1 microbicide studies as this level of product exposure exceeds the likely frequency of gel administration during efficacy studies, which will be driven by coital frequency.

2.18.4 Rationale for Change in Study Design

MTN-004, Version 2.0 was paused in October 2007 because five of the seven women that had enrolled into the study had experienced some signs and symptoms of genital irritation which were considered to be likely related to their use of the study products. These signs and symptoms were all mild and included vaginal dryness, vulvovaginitis, erythema, pelvic pain, cervical peeling, metrorrhagia, vaginal laceration and vaginal burning sensation, and lasted between 0-16 days (mean 5 days). An interim review of all available data at the time, including laboratory and clinical information, on the seven women who had been enrolled was then conducted. The review was blinded. This assessment confirmed that these signs and symptoms were minor in nature and typical for a Phase I microbicide study. They all resolved completely and rapidly during follow-up. A third study arm is being added and enrollment increased to provide more comprehensive data about the safety of these products that will strengthen the study conclusions. The third study arm will receive HEC gel as an inert placebo to assess the safety and tolerability of VivaGel[®] and the VivaGel[®] placebo, or “vehicle gel.”

3 OBJECTIVES

3.1 Primary Objective

- To assess the safety of VivaGel[®] when administered for 14 consecutive days on the vulvar and cervicovaginal mucosa of healthy sexually active HIV-negative women aged 18 – 24 years.

3.2 Secondary Objectives

- To assess the adherence to a short-term regimen of VivaGel[®] among healthy sexually-active HIV-negative women aged 18 – 24 years.
- To evaluate product acceptability among healthy sexually-active HIV-negative women aged 18 – 24 years.
- To assess the effect of a twice daily short-term regimen of VivaGel[®] on the vaginal microflora of healthy sexually-active HIV-negative women aged 18-24 years.

3.3 Exploratory Objectives

- Determine the pattern of cytokine/chemokine, innate immune factor changes, and functional activity associated with use of VivaGel® in the lower reproductive tract of healthy sexually active HIV-negative women aged 18 – 24 years.
- Determine the extent of SPL7013 absorption into the blood following the completion of product dosing.
- To assess the effects of VivaGel® on colposcopic findings

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-004 is a two site, Phase I, double blind, randomized, controlled comparison with 14 days of twice daily exposure to VivaGel®, VivaGel® placebo, or HEC gel, and follow-up among HIV-uninfected sexually active women. Participants in all three arms will receive male condom counseling and free male condoms on an ongoing basis. The study will be conducted at two sites: University of South Florida and University of Puerto Rico.

Table 7: Study Design

Arm	Description	N	Frequency
1	VivaGel® daily use	*18	Twice daily for fourteen consecutive days
2	VivaGel® placebo daily use	*18	Twice daily for fourteen consecutive days
3	HEC gel daily use	18	Twice daily for fourteen consecutive days

*Arms 1 and 2 will each have a final N between 18 and 25.

4.2 Summary of Major Endpoints

Primary Endpoints

- Abnormal genital symptoms judged by the Investigator to be possibly, probably, or definitely related to product use
- Abnormal pelvic exam findings (excluding findings observed by colposcopy only) judged by the Investigator to be possibly, probably, or definitely related to product use
- Grade 3 or higher laboratory values (as defined by the DAIDS Toxicity Tables) for hematology, liver function, creatinine level and coagulation judged by the Investigator to be possibly, probably, or definitely related to product use

- Adverse experiences judged by the Investigator to be possibly, probably, or definitely related to product use

Secondary Endpoints

Consistent with the secondary study objectives to assess adherence to, and acceptability of, a short-term regimen of VivaGel[®], and to assess the effect of this regimen on vaginal microflora, the following endpoints will be assessed:

- The proportion of participants who report via adherence questionnaire that they were adherent to the product use regimen, with adherence defined as the application of at least 80% of the expected number of doses of study product over the two weeks of product use;
- The proportion of participants who at their Two-Week Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during sexual intercourse in the future;
- Reported positive and negative aspects of using study product;
- Changes in vaginal flora.

Exploratory Endpoints

- Changes in cervical cytokine, innate immune factor (secretory leukocyte protease inhibitor (SLPI) and lactoferrin) expression, and functional activity (antiviral and antibacterial) in cervicovaginal secretions;
- Detection of SPL7013 in blood samples at Day 0 and Two-Week Clinic Visit (Target Day 14);
- Assessment of colposcopic findings.

4.3 Description of Study Population

The study population will include 18 to 24 year old US women who are HIV-negative, non-pregnant, sexually active, and healthy with a normal genital tract who are using adequate contraception.

4.4 Time to Complete Enrollment

The approximate time to complete study enrollment is expected to be nine months.

4.5 Study Groups

Three study arms including a total of 61 women are planned. Of these 61 women seven were randomized at a 1:1 ratio to VivaGel[®] or VivaGel[®] placebo, and a total of approximately 54 women will be randomized at a 1:1:1 ratio stratified by site to VivaGel[®] VivaGel[®] placebo, or HEC gel, with all three groups applying the product vaginally twice daily (approximately every 12 hours) for 14 days. Additional participants may be enrolled to ensure that a total of approximately 61 evaluable participants complete the three-week study.

4.6 Sequence and Duration of Trial Periods

Table 8: Sequence and Duration of Trial Periods for Individual Participants

Screening 1 Visit	Screening 2 Visit	Enrollment Visit	1-Week Clinic Visit	2-Week Clinic Visit	3-Week Clinic Visit
DAY -36 or less		DAY 0	DAY 6-8	DAY 13-15	DAY 20-24

Table 9: Projected Sequence and Duration of Trial Periods for MTN-004 Version 3.0

Enrollment Period	Follow-Up Period	Total Duration
9 months	1 month	10 months

4.7 Expected Duration of Participation

The expected duration of participation for individual enrolled participants is 21 days. Participants who have Adverse Events (AEs) which are not resolved at the 3-Week/Early Termination Visit will be followed beyond the 3-Week/Early Termination Visit until a clinically acceptable resolution of the AE(s) (at the discretion of the Site PI or NIH Medical Monitors) has been documented, including resolution date, if possible. No further study data (for purposes of data analysis) will be collected for these participants after the 3-Week/Early Termination Visit, except in cases of pregnancy to capture data on pregnancy outcome. In the unlikely event that a participant is pregnant at the time of her 3-Week/Early Termination Visit, sites will make every attempt to follow the participant until documentation can be completed regarding her pregnancy outcome.

4.8 Sites

Two study sites are planned for this trial: University of South Florida and University of Puerto Rico.

5 STUDY POPULATION

5.1 Selection of the Study Population

A total of 61 healthy, non-pregnant, sexually active, HIV-negative women of the ages 18 through 24 years inclusive with a normal genital tract who are using adequate contraception will be enrolled in this study. For the purposes of MTN-004, “normal” is defined as:

- Anatomically normal pelvic exam at Screening 1, according to clinical judgment of the examiner
- Without evidence of genital infection at Screening 1, as defined by eligibility criteria
- Without evidence of deep disruption of the genital epithelium at Screening 1

Participants will be recruited from a variety of venues. There are two sites: University of South Florida and University of Puerto Rico. Each site will enroll approximately 30 participants. Additional participants may be enrolled if non-adherent participants need to be replaced or if enrollment “slots” need to be shifted from one site to another.

5.1.1 Composition

It is anticipated that the study population will be primarily composed of Hispanic-Latina female volunteers, although women of all racial/ethnic backgrounds will be included. As this study is primarily examining the safety of a vaginally applied product, only female volunteers will be enrolled.

5.1.2 Recruitment

Members of the research teams at both study sites will recruit women from various clinical sites at which they are providing direct patient care to potential study participants. Study staff will contact volunteers from previous research studies if those participants have previously signed an authorization permitting this type of contact. Site IRB-approved media advertisements, telephone scripts, and fliers will be used. These materials will be presented and discussed with the community advisory boards at both sites before submission to the local IRBs. Written informed consent will be obtained prior to the initiation of any study-related procedures.

5.1.3 Retention

Each site will establish participant retention procedures to target an average retention rate of 95% at 3 weeks. Study site staff members at each site are responsible for developing and implementing site-specific SOPs to target this goal.

5.1.4 Co-Enrollment Guidelines

Women with participation in any other investigational drug trial in the 30 days prior to enrollment will not be enrolled in this study. Study participants will be required to refrain from enrollment in other clinical trials involving investigational or prohibited drugs during their involvement in this study. Participants who report after enrollment their concurrent participation in such trials will be discussed by the PSRT and may be discontinued from use of study product. In this case they will be encouraged to remain in the study and will be followed with all safety evaluations deemed clinically appropriate by the Investigator and the NIH medical monitor.

5.2 Inclusion Criteria

- Age 18-24 years at screening and enrollment, inclusive, and verified per site SOP. For the Puerto Rico site, participants aged 18-20 years will be eligible if legally emancipated, with relevant local IRB waiver, or with parental consent.
- Willing and able to provide written informed consent for screening and enrollment
- General good health as determined by the site clinician at screening and enrollment
- HIV-uninfected (per HIV Antibody Testing Algorithm, Appendix III)
- Normal Pap result at screening or able to document normal result from Pap done within the 12 calendar months prior to screening
- Predictable menstrual cycle, per participant report, with ≥ 21 days between menses (does *not* apply to participants who report using a hormonal method of contraception at enrollment, e.g., Depo-Provera)
- Sexually active (penile-vaginal intercourse by participant report at a minimum average of one episode per week in the 30 days prior to screening) and intention to continue penile-vaginal intercourse at the same approximate frequency for the duration of study participation
- Willing to abstain from oral-vaginal and penile-anal intercourse for the duration of study participation.
- Visualization of vaginal and cervical anatomy that, in the clinical judgment of the colposcopist, lends itself to colposcopy
- Use of an effective method of contraception at enrollment, and intention to use effective method of contraception for the duration of study participation including one month after finishing study product application. Effective method of contraception is defined as either hormonal method (except vaginal ring); IUD inserted at least 30 days prior to enrollment; sterilization; or sexual activity with documented vasectomized partner(s)
- Willing to abstain from the use of other intravaginal products and/or devices including sex toys from 72 hours prior to enrollment through the 3-Week/Early Termination Visit
- Willing to use VivaGel[®], VivaGel[®] placebo, or HEC gel as required by protocol
- Agree to not participate in other drug or device study during study participation
- Urine negative for pregnancy test at screening and enrollment

- Agree to have partner use study provided condoms for each act of intercourse during study participation
- Willing to participate as required by protocol, including assessments and follow-up schedule

5.3 Exclusion Criteria

- History of adverse reaction to latex or to any component of the study products
- Reported history of male sex partner having an allergic reaction to latex
- Using a diaphragm, vaginal ring, and/or spermicide for contraception at enrollment, and/or intention to use a diaphragm, vaginal ring, and/or spermicide for contraception during study participation
- Pregnant or breastfeeding at screening or enrollment, or has had any form of pregnancy within 90 days of enrollment
- Grade 3 or higher liver function, creatinine, coagulation, or hematology abnormality in accordance with DAIDS toxicity table values (normal values based on site specific laboratory criteria) at screening and confirmed by retest/and or redraw
- Gynecologic surgical procedure in 90 days prior to enrollment (e.g., biopsy, tubal ligation, dilation and curettage, etc.)
- Any abnormal finding on physical or pelvic examination, which, in the opinion of the investigator, precludes participation in the trial (including anatomical abnormalities,, non-iatrogenic colposcopic findings involving deep disruption of the epithelium, and inflammation of the vulva, vagina, or cervix); women with HPV warts exterior to labia minora requiring treatment will be excluded
- Sexually transmitted infection (STI) or reproductive tract infection (RTI) according to the 2006 Center for Disease Control (CDC) guidelines via lab tests at screening, or examination at screening or enrollment, and requiring treatment, including symptomatic bacterial vaginosis (BV) (clinical criteria or Gram stain evidence plus symptomatic discharge, odor, or itching), symptomatic candidiasis, other vaginitis, trichomoniasis, Chlamydia, gonorrhea, syphilis, active HSV lesions (HSV-2 seropositive not excluded except with active lesions), chancroid, pelvic inflammatory disease (PID), genital sores or ulcers, cervicitis, genital warts of the labia minora, vagina, or cervix, or any other symptomatic genital warts. *Note: Signs of asymptomatic BV may include the presence of white to grey homogeneous discharge, positive whiff test (amine odor) with addition of potassium hydroxide (KOH), pH greater than 4.5, presence of clue cells, a decrease in lactobacilli morphotypes, and increase in non-lactobacilli morphotypes. Women with clinical criteria or evidence of BV and with symptoms (symptomatic discharge, odor, itching) will be excluded. Women without symptoms, but with clinical or laboratory evidence of BV, are still eligible.*
- In the six months prior to enrollment, diagnosed with or treated for any STI (except genital HSV recurrence) or pelvic inflammatory disease
- Use of oral and/or vaginal preparations of antibiotic or antifungal medications, at Screening or within 30 days prior to the enrollment visit
- Participation in any other drug or device study within 30 days prior to enrollment visit
- Injected non-therapeutic drugs in the 12 calendar months prior to enrollment

- At screening or enrollment, any social or medical condition that, in the investigator's opinion, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

6 STUDY PRODUCT

6.1 Regimen

The regimen for the study products will be as follows:

Table 10: Study Product Regimen

Arm	Description	N	Dose, Route, and Frequency
1	VivaGel [®] daily use	*18	One 3.5 g applicator per vagina twice daily for fourteen consecutive days
2	VivaGel [®] placebo daily use	*18	One 3.5 g applicator per vagina twice daily for fourteen consecutive days
3	HEC gel daily use	18	One 3.5 g applicator per vagina twice daily for fourteen consecutive days

*Arms 1 and 2 will each have a final N between 18 and 25.

Study staff will instruct participants on the proper methods of storing and applying the products. Beginning on Day 0, participants in all three arms of the study will utilize one single-dose, pre-filled applicator containing 3.5 g of study product (VivaGel[®], VivaGel[®] placebo, or HEC gel) twice daily, for fourteen consecutive days. The participant will insert the first dose of study product at the Enrollment Visit. Target doses are in the morning and in the evening (approximately every 12 hours). The evening dose should be administered before longest period of rest (usually night).

If a participant misses a dose, she should make up the missed dose as soon as possible, unless the next application is due within 2 hours or less. If the next dosing time is in 2 or less hours, then the missed dose should not be made up; rather, the participant should wait until the next dosing time to insert the study gel.

Participants may continue their usual hygiene practices with the exception of any products applied directly to the vulva or vagina. In particular, participants will be educated and counseled about the risks of douching and advised to avoid this practice. Participants will be informed that tampons, sanitary pads, swimming, bathing, and sauna use are permitted. Participants will be advised to not use other participants' study gel, or to distribute their own study gel to other women. Study participants will be instructed to wash their hands before and after using the applicator to insert study gel.

6.2 Study Product Supply and Accountability

6.2.1 Study Product Supply

VivaGel[®] and VivaGel[®] placebo are manufactured and packaged in single-use applicators and analyzed/released under current good manufacturing practices (cGMP).

HEC gel will be manufactured, analyzed/released, and packaged in single-use applicators under good manufacturing practices (cGMP).

VivaGel[®], VivaGel[®] Placebo, and HEC Gel Applicators

This study will utilize test article packaged in identical, pre-filled, opaque white, single-use plastic applicators containing 3.5g of the study products (VivaGel[®], VivaGel[®] placebo or HEC gel). Both active and placebo gels are clear and are of similar viscosity. Each product (VivaGel[®], VivaGel[®] placebo, and HEC gel) will be packaged in cartons containing 10 pre-filled, single use applicators per carton.

The applicator measures approximately 11.4 cm long and 1.05 cm wide, and has a barrel-and-plunger design with screw-on cap to be removed before product usage. The applicator has a tapered, rounded tip for easy insertion into the vagina. A mechanism on the applicator prevents refilling and reuse. The seal inside the barrel is made from non-latex rubber. The same type of applicator is widely used for other vaginal products, including Monistat[®].

6.2.2 Study Product Receipt

Site pharmacists will be required to maintain complete study records of all study product supplies received. These records will contain documentation of receipt as well as dispensing of all study supplies

6.2.3 Storage

In accordance with documented 12-month stability data, VivaGel[®] and VivaGel[®] placebo should be stored in the single-use, pre-filled polypropylene applicators at 20-25°C (68-77°F) for up to 12 months, with short-term excursions allowed between 15-30°C (59-86°F) in storage/shipping. VivaGel[®] has been shown to be stable in the vaginal applicators for up to 9 months at 40°C (104°F). The HEC gel should be stored at room temperature (15-30°C).

Storage conditions for protocol-provided study products will include segregation, security, and temperature monitoring, as well as appropriate conditions of light, moisture, ventilation and sanitation. Study products should be stored in a limited access area that is locked when not in use. The study products should be accessible only to authorized personnel, such as the Pharmacist of Record and his/her pharmacist designee.

Study participants will be instructed to store their applicators at the recommended storage conditions, and away from direct sources of light and heat, in an area out of reach of children. Study products will be stored in accordance with the protocol.

6.2.4 Dispensing

Study products will be dispensed only to enrolled study participants, or to study staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. An authorized prescriber includes the Investigator of Record (IoR) or a licensed clinician directly responsible to the IoR as noted on the FDA 1572.

Twenty individually wrapped pre-filled applicators dispensed in two cartons of ten applicators each will be provided at the Enrollment Visit. At the One-Week Clinic Visit, participants will receive an additional carton containing ten applicators.

Participants will be instructed to contact the study site to request additional supplies in the event that additional supplies between visits are needed. All circumstances resulting in this additional supply will be documented fully by the Site Principal Investigator or designee. The pharmacist will record the dispensing of any additional study product on the documents maintained by the Pharmacist of Record or designee.

6.2.5 Accountability

Study product accountability will be performed and documented. The study pharmacist must maintain complete records of study gel as well as study gel re-supply, transfers, chain of custody (e.g., record if dispensed directly to patient or other study staff), returns, destruction (if applicable), and other related issues as outlined in the Pharmacy Instructions Manual for the MTN Clinical Trials.

6.2.6 Retrieval of Unused Study Products

Study participants will be instructed to bring all unused study products back to the enrollment site at the Two-Week Clinic Visit. In the event that unused study products are not returned to the enrollment site, study staff members will make attempts to retrieve unused study products. All unused study products must be returned to the site and then forwarded to the MTN CORE after the study is completed or terminated unless otherwise instructed by the MTN CORE.

6.3 Assessment of Participant Adherence

Data on adherence to self-administration of a study gel will be collected at the Two-Week Clinic Visit via a web-based questionnaire (see acceptability and adherence questionnaire in Section 7.2, Behavioral Measures). This questionnaire will collect data on the number of times participants used the gel during the trial and reasons that may have prevented participants from adhering to protocol requirements.

Adherence counseling will be provided to all study participants upon enrollment into the study, and as needed thereafter to help ensure high rates of study product use. Counseling will include client-centered strategies to remember to use the product as directed both in the home and away from home. In addition, counseling will cover the importance of contacting study staff with questions about study product use and requests for additional supplies. For participants who anticipate or report adherence difficulties at the One-Week Clinic Visit, every effort will be made to identify strategies that will help increase their rates of correct product use throughout participation in the study. Section 10 outlines how data on participant adherence will be incorporated into analysis of the study results.

6.4 Concomitant Medications and Procedures

Throughout the course of the study, all concomitant medications, including those used to treat AE's, will be recorded in the participant's chart on forms designed for that purpose. Prescription medications, over-the-counter preparations, vitamins and nutritional supplements, and herbal preparations will all be recorded as concomitant medications. Medications/procedures not listed below under precautionary and prohibited medications and procedures are permitted.

6.4.1 Permitted Medications and Procedures

With the exception of those not permitted under inclusion/exclusion criteria, concomitant medications will be permitted. These include both prescription and non-prescription medications.

6.4.2 Prohibited Medications and Procedures

Several concomitant medications/devices will not be permitted, including spermicides, diaphragms, contraceptive vaginal rings, and oral and vaginal preparations of antibiotic or antifungal medication. These medications will be not allowed in order to protect the integrity of the lower genital tract and reduce the possibility of adverse events due to agents other than the study gel and applicator. Oil-based lubricants are also known to risk damage to the integrity of latex male condoms and are prohibited.

Potential participants who report current or recent use of these medications will not be enrolled in the study. Participants already enrolled who report concurrent use will be reviewed by the PSRT and may be discontinued from study product use. These participants will continue to be followed for safety assessment through study exit. All concomitant medications will be recorded on Concomitant Medication records.

6.4.3 Precautionary Medications and Procedures

There are no known precautions for concomitant use with the study products/interventions.

6.4.4 Required Medications and Procedures

Latex male condom use is required for all acts of penile vaginal intercourse by participants enrolled in this study. As noted above, latex male condoms will be provided to participants.

Male condoms

Both study site pharmacies will be provided with a single brand of lubricated male condoms by MTN CORE to distribute to participants in quantities expected to be sufficient according to study-specific procedures when study product is dispensed. These male condoms will not be impregnated or coated with any type of spermicide. Male condoms will be required for all sexual encounters with a male partner during the study period. In the event that a participant needs additional male condoms between visits, she may request these from study sites at any time. Participants will be provided with a list of approved brands that can be used in place of the study provided condoms to help encourage condom use by their male partners.

Panty Liners and Pads

Both study site pharmacies will be provided with single brands of panty liners and pads by the MTN CORE to distribute to participants in quantities expected by the participant to be sufficient when study product is dispensed. In the event that a participant needs additional panty liners or pads between visits, she may request these from study sites at any time. It is hoped that women enrolled in the study will not be menstruating during the two weeks of study drug administration. However, if women do menstruate they will be able to use sanitary towels or tampons of their own choice.

7 STUDY PROCEDURES

This section outlines study procedures according to visit schedule for participants. The study visits included here are the Screening 1 Visit, Screening 2 Visit, 1-Week Clinic Visit, 2-Week Clinic Visit, 3-Week Clinic Visit, and the Safety Visits.

7.1 Clinical Evaluations and Procedures

- Medical history, including medical-surgical history, allergy history, menstrual history, contraception use
- Medications history, including current prescription and non-prescription medications
- Counseling procedures, including condom use counseling, HIV pre- and post-test counseling, other laboratory test results counseling
- Questionnaires, including adherence, sexual behavior, history of vaginal product use, product acceptability
- Vital signs, including heart rate, blood pressure, and temperature

- Abdominal exam, including inspection and palpation
- Pelvic exam, including speculum exam and bimanual exam
- Colposcopic exam

7.2 Behavioral Measures

Each study site will have a computer terminal connected to the Web that the participants will use three times during the study to respond to Behavioral Measures. This computer terminal will be placed in such way to assure the confidentiality of the participants' responses (i.e. the screen will be out of site of staff members or other participants while answers are being entered). Behavioral Measures will be the Baseline Behavioral Questionnaire, taken at the Enrollment Visit, the Acceptability and Adherence Questionnaire, taken at the 2-Week Clinic visit, and the Study Burden Questionnaire taken at the 3-Week Clinic Visit (see Appendix I, Schedule of Study Visits and Evaluations).

7.2.1 Baseline Behavioral Questionnaire

A staff member will access the Web page for the questionnaire and enter a password to log in. Next, the staff member will enter the participant's ID and date and let the participant complete the rest of the questionnaire. Initially, the participant will be presented simple practice questions (e.g., "choose all that applies," "indicate how many times," "choose one of a fixed set of answers"). Once the practice has been successfully completed, the participant will read a statement encouraging her to respond to all questions as truthfully as possible. Next, she will proceed to the Baseline Behavioral Questionnaire. This questionnaire will assess different types of sexual behavior (vaginal/anal/oral), condom use per act (with/without), partner gender (male/female), partner type (significant other/casual partner), and partner HIV status (positive, negative, unknown) in the recent past. It will also include questions on past use of vaginal hygiene products, medications, desiccants, douches, tampons, and vaginal pregnancy prevention methods. Participants will also be asked to report on substance use, and likelihood of using a microbicide in the future.

7.2.2 Acceptability and Adherence Questionnaire

At the Two-Week Clinic Visit, the participant will once again fill in a Web-based survey. This time it will be the Acceptability and Adherence Questionnaire that will explore the experiences the participant had during the prior 14 days using the gel vaginally, her likes and dislikes concerning the gel, the applicator, the application process, any changes she may have introduced or may wish to introduce in the volume used, any problems (e.g. leakage) she may have had, partner's reaction, sexual enjoyment, condom use during sexual intercourse using the gel, changes in her habitual sexual behavior, and likelihood of using a microbicide in the future. This last section will have items worded very similar to those of the same section applied at baseline, so that

comparisons can be made regarding the anticipated likelihood of future microbicide use before and after becoming familiarized with the product.

7.2.3 Study Burden Questionnaire

At the Three-Week Clinic Visit, the participant will complete the final Web-based survey, the Study Burden Questionnaire that will explore through close-ended questions the participant's overall experiences during the trial, and her likes and dislikes.

If any participant discontinues trial participation, she will be encouraged to respond to the Acceptability and Adherence Questionnaire and the Study Burden Questionnaire at the time of trial discontinuation.

7.3 Laboratory Evaluations

- Urinalysis
- Qualitative urine pregnancy test
- Urine SDA for *N. gonorrhoeae* and *C. trachomatis*
- HIV antibody screen
- Rapid plasma reagin (RPR)
- Complete blood count (hemoglobin, WBC with differential, platelets)
- Liver function panel (AST, ALT)
- Creatinine level
- Coagulation panel (PTT and INR)
- Plasma SPL7013 level
- Pap smear of cervix unless documented normal Pap available within the last year
- Vaginal swab pH
- Vaginal wet preparation slide for yeast, bacterial vaginosis, and trichomoniasis
- Gram-stained vaginal smear
- Quantitative vaginal cultures
- Cervical cytokine panel and innate immune factors (secretory leukocyte protease inhibitor (SLPI) and lactoferrin)
- As clinically indicated: urine culture and sensitivity, herpes culture, Genprobe Aptima, rapid plasma reagin (RPR), treponemal confirmation, HIV Western blot

7.4 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical practice, the MTN Network Laboratory Manual, the study-specific procedures manual, and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented using the Laboratory Data Management System (LDMS).

The MTN Network Laboratory has confirmed that the study gels do not inhibit or otherwise interfere with the pregnancy test and dipstick urinalysis methodology selected for this study. The study gel has been determined to interfere with SDA testing for Chlamydia and gonorrhea. Chlamydia and gonorrhea testing is only done at Screening, unless indicated at follow-up visits; in these cases, the testing will be done via Genprobe Aptima, which has been determined to be unaffected by the study gel.

7.4.1 Local Laboratory Specimens

The following types of specimens will be collected at the study site and tested at the local laboratory: urine, vaginal, cervical, blood, and (as needed) other pelvic swabs.

Urine Samples

The Local Laboratory or Site Research Staff will perform urinalysis and pregnancy tests.

Vaginal Samples

The Local Laboratory or Site Research Staff will test vaginal swabs for bacterial vaginosis, candidiasis, and trichomoniasis.

Cervical Samples

The Study Site Laboratory will examine ectocervical and endocervical Pap smear specimens.

Other Pelvic Samples

The Local Laboratory will test pelvic swabs for HSV-2 via culture as needed.

Blood Samples

Study site staff will collect blood samples for the following testing at the local laboratory: complete blood count, liver function, creatinine level, and coagulation testing. Study site staff or Local Laboratory staff will also obtain blood for HIV-1 Antibody Test, and perform testing per SOP.

7.4.2 Starpharma Laboratory Specimens

Plasma samples will be assayed for SPL7013 levels using a validated capillary electrophoresis bioanalytical method at the Starpharma Pty Ltd bioanalytical laboratory in Melbourne, Australia.

7.4.3 Network Laboratory Specimens

Vaginal and cervical specimens listed below will be collected at the study site and tested at the MTN Network Laboratory. These include: vaginal gram stain, quantitative vaginal cultures, cervical cytokines, cervical innate factors, and urine SDA for *C. trachomatis* and *N. gonorrhoeae* testing. As indicated, Genprobe Aptima testing may be performed on urine specimens for the detection of Chlamydia and gonorrhea.

Vaginal Specimens

The assessment of vaginal flora will be based on the Nugent Scoring System for Gram-Stained Vaginal Smears as well as assessment of several groups of organisms. These organisms will include *Lactobacillus* species, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, anaerobic gram-negative rods (Bacteroides, Prevotella, Porphyromonas), Enterococcus species, Group B Streptococcus, and Candida species.

Gram-stained vaginal smears will have leukocytes quantified according to Network Laboratory SOP.

Cervical Specimens

Cervical cytokines and innate factors will be handled and measured according to policies outlined in the SSPs for this study. Cytokines to be measured include: IL-1 β , IL-6, GM-CSF, TNF- α , IFN- γ , MIP-1 α , and IL-12p40. Cytokines will be measured according to Network Laboratory SOP via the Luminex[®] 100TM Instrument (Luminex Co., Austin, TX), using concentrations extracted from an 8-point standard curve via the Luminex[®] 100TM IS software. Cervical innate factors (SLPI and lactoferrin) will be measured by ELISA. Levels of cytokines and innate factors will be correlated to functional assays that will measure the anti-viral (HSV-2) and anti-bacterial (*Escherichia coli* and *Staphylococcus aureus*) activity as a surrogate marker of mucosal immunity. These activities will be measured according to policies outlined in the SSPs.

Urine Specimens

C. trachomatis and *N. gonorrhoeae* will be detected using an amplified DNA (SDA) assay and measured according to policies outlined in the SSP. As indicated, Genprobe Aptima testing may be performed on urine specimens for the detection of Chlamydia and gonorrhea.

7.4.3.1 Quality Control and Quality Assurance Procedures

Network Laboratory staff will conduct visits as needed to both sites to assess the implementation of on-site laboratory quality control procedures, including the proper maintenance of laboratory testing equipment, etc.

7.4.3.2 Specimen Storage and Possible Future Research Testing

Plasma and cervical specimens will be stored at the MTN Network Laboratory for possible future research testing. The informed consent process will include appropriate consent to obtain and store these samples.

7.5 Specimen Preparation, Handling, and Shipping

All specimens will be shipped in accordance with International Air Transport Association (IATA) specimen shipping regulations. All shipments will be documented using the LDMS. Details on specimen preparation, handling, shipping, and biohazard containment are included in the SSP.

7.6 Sequence of Procedures/Evaluations

Protocol Appendix I summarizes the expected sequence of procedures and evaluations for MTN-004. Upon indicating interest in the study, a brief telephone-screening interview with the prospective participant may be conducted to determine participant preliminary eligibility for this study.

7.6.1 Screening 1 Visit

The Screening 1 Visit may occur up to Day-36 of enrollment. Written informed consent will be obtained prior to the onset of any study procedures, in concordance with Good Clinical Practices, and after a thorough discussion of risks, benefits and alternatives. Further information on the informed consent process is in the MTN Manual of Procedures.

Table 11: Screening 1 Visit

Screening 1 Visit (within -36 days)	
Component	Procedure/Analysis
Study Communications	<ul style="list-style-type: none"> • Explain study requirements • Informed consent document • Assign Participant ID (PTID) • Collect contact information • Collect demographic information • Administer behavioral eligibility assessment • Collect medical and menstrual history • Provide HIV pretest and post-test counseling • Provide male condom counseling • *Treat or refer for treatment and/or further counseling (including STI treatment and/or counseling) • Schedule Screening 2 Visit as appropriate • Provide reimbursement for study visit
Urine	<ul style="list-style-type: none"> • Pregnancy test • Urinalysis • *Culture and sensitivity • SDA for GC/CT
Blood	<ul style="list-style-type: none"> • Complete blood count • Liver function panel • Creatinine level • Coagulation panel • Rapid Plasma Reagin/*Confirmatory testing • HIV-1 Antibody Test/*Confirmatory testing
Targeted Physical Exam	<ul style="list-style-type: none"> • Vital signs (temperature, blood pressure, pulse) • Abdominal exam
Pelvic Exam	<ul style="list-style-type: none"> • Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with leukocyte quantification • *Herpes culture • Pap smear (if no written report from prior year)

*If clinically indicated

7.6.2 Screening 2 Visit

The purpose of the Screening 2 Visit is to review with potential study participants their results from Screening 1, as well as to ensure that eligibility criteria are met before

scheduling an Enrollment Visit. The Screening 2 Visit will be scheduled to occur within 36 days of enrollment and can also occur on the same day as the Enrollment Visit.

Table 12: Screening 2 Visit

Screening 2 Visit (within -36 days)	
Component	Procedure/Analysis
Study Communications	<ul style="list-style-type: none"> • Update contact information • Update medical and menstrual history • Administer behavioral eligibility assessment • Male condom counseling • Provide other test results as available, with associated counseling • When clinically indicated, treat or refer for treatment and/or further counseling (including STI treatment and/or counseling) • Schedule follow-up appointment as appropriate. If participant is eligible for enrollment, conduct Enrollment Visit or schedule Enrollment Visit for a later date (within the 36-day window). • Provide reimbursement for study visit
Laboratory Measures	<ul style="list-style-type: none"> • Pregnancy test • *Repeat collection of screening laboratory specimens

*only in cases where sample was judged to be inadequate, or in cases of no result

7.6.3 Enrollment Visit

The Enrollment Visit will take place at or less than 36 days following the Screening 1 Visit, approximately 1 to 2 days after the complete cessation of menses. The Screening 2 Visit and the Enrollment Visit can also occur on the same day.

Table 13: Enrollment Visit

Enrollment Visit (Day 0)	
Component	Procedure/Analysis
Study Communications	<ul style="list-style-type: none"> • Explain study requirements • Informed consent document • Administer informed consent comprehension test • Record concomitant medications • If Enrollment does not take place on the same day as the Screening 2 Visit: <ul style="list-style-type: none"> ○ Update contact information ○ Re-assess eligibility** ○ Update medical and menstrual history • Provide test results as available, with associated counseling • *Treat or refer for treatment and/or further counseling (including STI treatment and/or counseling) • Provide study product usage instructions • Schedule 1-Week Clinic Visit • Provide reimbursement for study visit
Behavioral Measures	<ul style="list-style-type: none"> • Administer baseline behavioral and vaginal product use questionnaire
Urine	<ul style="list-style-type: none"> • *Pregnancy test (required only if Enrollment does not take place on the same day as the Screening 2 Visit) • *Urinalysis • *Culture and sensitivity • *SDA for GC/CT
Blood	<ul style="list-style-type: none"> • Complete blood count • Liver function panel • Creatinine level • Coagulation panel • SPL7013 level • *Rapid Plasma Reagin/*Confirmatory testing • Plasma archive
Targeted Physical Exam	<ul style="list-style-type: none"> • Vital signs (temperature, blood pressure, pulse) • Abdominal exam
Pelvic Exam	<ul style="list-style-type: none"> • Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with leukocyte quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • Colposcopy of vulva, vagina, and cervix

Randomization	<ul style="list-style-type: none"> • Follow study-specific procedures for randomization
Study Supplies	<ul style="list-style-type: none"> • Dispense two cartons (20 applicators) of study gel, male condoms and panty liners, and/or pads, and resealable plastic bags • Participant to insert first dose in study clinic

*If clinically indicated

** In the event that Enrollment does not take place on the same day as the Screening 2 Visit, the following screening procedures must additionally be completed on the day of Enrollment to confirm participant eligibility prior to Enrollment:

- Review of all prior screening documentation, with update of medical and menstrual history and/or current medications if applicable
- Review contact information and update as necessary
- Re-confirmation (by participant self-report) that participant is not currently using other intravaginal products, and is not planning to use other intravaginal products during her study participation
- Re-confirmation that the participant has not used prohibited products as outlined in Section 6.4.2 in the last 30 days
- Re-confirmation (by participant self-report) that participant has not participated in any other drug or device study in the last 30 days, and is not planning to participate in any other drug or device study during her study participation
- Re-confirmation (by participant self-report) that participant is currently using an effective method of contraception (hormonal method (except vaginal ring), IUD inserted at least 30 days prior to Enrollment, sterilization, or sexual activity with a documented vasectomized partner) and plans to do so for the duration of her study participation
- Re-confirmation (by participant self-report) that participant is not currently using a diaphragm, vaginal ring, and/or spermicide for contraception, and does not plan to use these for the duration of her study participation
- Re-confirmation (by participant self-report) that the participant has not been diagnosed with or treated for any STI (except genital HSV recurrence) or pelvic inflammatory disease in the last 6 months
- Pregnancy test
- Male condom counseling
- Re-confirmation (by participant self-report) that the participant has not been pregnant, given birth, or had a pregnancy outcome, and has not breastfed in the last 90 days
- Re-confirmation (by participant self-report) that the participant has not had a gynecological surgical procedure in the last 90 days
- Re-confirmation (by participant self-report) that the participant has not injected non-therapeutic drugs in the last 12 calendar months
- Any other clinically indicated behavioral, clinical, or laboratory assessments

7.6.4 Phone Assessment

For the Phone Assessment, study staff will ask participants if they are having any difficulty with the study gel or applicator, and review applicator and/or study product-related instructions as needed. Any adverse events will be recorded and followed with safety visits if deemed necessary by the site investigator. This contact may be initiated by study staff or the participant on Study Day 2-4 (Target Day 2), as agreed upon prior to the call.

7.6.5 One-Week Clinic Visit

The One-Week Clinic Visit is outlined below. The One-Week Clinic visit will take place within the window of Days 6-8 post enrollment.

Table 14: One-Week Clinic Visit

<i>One-Week Clinic Visit (Day 6-8)</i>	
Component	Procedure/Analysis
Study Communications	<ul style="list-style-type: none"> • Update contact information • Update medical and menstrual history • Update Concomitant Medications Form (if applicable) • Record Adverse Events (if applicable) • Male condom counseling • Provide test results as available, with associated counseling • *Treat or refer for treatment and/or further counseling • Reinforce study product usage instructions • Schedule 2-Week Clinic Visit • Provide reimbursement for study visit
Behavioral Measures	<ul style="list-style-type: none"> • Administer adherence assessment
Urine	<ul style="list-style-type: none"> • Pregnancy test • *Urinalysis • *Culture and sensitivity • *Genprobe Aptima for GC/CT
Blood	<ul style="list-style-type: none"> • Complete blood count • Liver function panel • Creatinine level • Coagulation panel • *Rapid Plasma Reagin/*Confirmatory testing
Targeted Physical Exam	<ul style="list-style-type: none"> • Vital signs (temperature, blood pressure, pulse) • Abdominal exam

Pelvic Exam	<ul style="list-style-type: none"> • Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with leukocyte quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • *Colposcopy of vulva, vagina, and cervix • *Herpes culture
Study Supplies	<ul style="list-style-type: none"> • Count returned unused applicators • Dispense one carton (ten applicators) of study gel • Dispense more male condoms and panty liners and/or pads if needed

*If clinically indicated

7.6.6 Two-Week Clinic Visit

The Two-Week Clinic Visit is outlined below. The Two-Week Clinic Visit will take place within the window of days 13-15 post enrollment

Table 15: Two-Week Clinic Visit

<i>Two-Week Clinic Visit (Day 13-15)</i>	
Component	Procedure/Analysis
Study Communications	<ul style="list-style-type: none"> • Update contact information • Update medical and menstrual history • Update Concomitant Medications Form (if applicable) • Record and/or update Adverse Events (if applicable) • Male condom counseling • Provide test results as available, with associated counseling • *Treat or refer for treatment and/or further counseling • Schedule 3-week Clinic Visit • Provide reimbursement for study visit
Behavioral Measures	<ul style="list-style-type: none"> • Administer acceptability assessment • Administer adherence assessment
Urine	<ul style="list-style-type: none"> • Pregnancy test • *Urinalysis • *Culture and sensitivity • *Genprobe Aptima for GC/CT
Blood	<ul style="list-style-type: none"> • Complete blood count • Liver function panel • Creatinine level • Coagulation panel • SPL7013 level

	<ul style="list-style-type: none"> • *Rapid Plasma Reagin/Confirmatory testing • Plasma archive
Targeted Physical Exam	<ul style="list-style-type: none"> • Vital signs (temperature, blood pressure, pulse) • Abdominal exam
Pelvic Exam	<ul style="list-style-type: none"> • Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with leukocyte quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • Colposcopy of vulva, vagina, and cervix • *Herpes culture
Study supplies	<ul style="list-style-type: none"> • Count returned unused applicators

*If clinically indicated

7.6.7 Three-Week Clinic/Early Termination Visit

The Three-Week Clinic Visit will be the final scheduled study visit at the study site and will take place within a five-day window (days 20-24 from enrollment). Any additional study visits will occur only on an as-needed basis as determined by study-specific criteria. Study staff will attempt to record resolution dates for any outstanding AEs and/or concomitant medications at this visit, if possible.

Table 16: Three-Week Clinic/Early Termination Visit

<i>Three-Week Clinic/Early Termination Visit (Day 20-24)</i>	
Component	Procedure/Analysis
Study Communications	<ul style="list-style-type: none"> • Update contact information • Update medical and menstrual history • Update Concomitant Medications Form (if applicable) • Record and/or update Adverse Events (if applicable) • Provide test results as available, with associated counseling • *Treat or refer for treatment and/or further counseling • Provide reimbursement for study visit • *Schedule additional visits to resolve ongoing adverse events
Behavioral Measures	<ul style="list-style-type: none"> • Administer Study Burden Assessment
Urine	<ul style="list-style-type: none"> • Pregnancy test • *Urinalysis • *Culture and sensitivity • *Genprobe Aptima for GC/CT

Blood	<ul style="list-style-type: none"> • *Complete blood count • *Liver function panel • *Creatinine level • *Coagulation panel • *Rapid Plasma Reagin/*Confirmatory testing
Targeted Physical Exam	<ul style="list-style-type: none"> • Vital signs (temperature, blood pressure, pulse) • Abdominal exam
Pelvic Exam	<ul style="list-style-type: none"> • Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears for leukocyte quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • *Colposcopy of vulva, vagina, and cervix • *Herpes culture
Study Supplies	<ul style="list-style-type: none"> • *Count returned unused applicators (if not already returned at previous visit)

*If clinically indicated

Note for all follow-up visits: If a participant has her menses at the time of her study visit, all visit procedures except the pelvic exam, colposcopy, and associated specimen collections should be performed at that time. The pelvic exam, colposcopy, and associated specimen collections required for the given visit may be rescheduled for a date as soon as practical after the end of the participant's menses.

7.6.8 Interim Contacts and Safety Visits

At any time during the study, a participant may be seen for an unscheduled visit if requested by the participant or deemed necessary by an investigator. Study staff will utilize case report forms designed especially for interim contacts and visits.

Participants will have a urine pregnancy test at each interim visit. If deemed necessary by the examining clinician, the participant will be scheduled for colposcopy. Participants reporting vaginal bleeding or spotting other than expected menstrual bleeding will be evaluated via colposcopy. Unexpected intermenstrual bleeding, unexpected menstrual bleeding (menorrhagia or metrorrhagia), bleeding associated with new or changed findings, and bleeding from no obvious source will be considered adverse events.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff or require additional study supplies. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs,

study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care; all AEs associated with genital symptoms will be evaluated according to the pelvic exam procedures described for the regularly scheduled follow up visits, and diagnosis and follow up of any observed abnormalities will proceed according to Appendix II.

7.7 Colposcopy

Experienced staff at both sites will conduct colposcopic examinations of the study participants. In addition, an MTN Safety Physician will provide specialized training in colposcopy for the evaluation of vaginal products.

7.8 Colposcopic Images

Records of digital colposcopic images are required for enrollment and for any findings at follow up visit examinations. The colposcopist will document findings in the participant's chart notes and on the study case report forms. When there are findings on follow-up visits, the clinician should retain digital video images in order to complement documentation of baseline findings, abnormal findings or injury. The informed consent document will include consent to obtain these digital images.

7.9 Final Contact

The Two-Week Clinic Visit for all participants will include laboratory testing for complete blood count, liver panel, creatinine level, and coagulation panel. If the results are not available at the Three-Week Clinic visit for participants, a final contact (in person or by telephone [except for HIV test results]) may be required to provide the final study test results, post-test counseling, and treatment from these visits. In addition, for participants who become pregnant prior to the study end date, an additional contact may be required to ascertain the participant's pregnancy outcome. Study sites may complete the final contact visit(s) at the study site or at community based locations, depending on site capacities and site and participant preferences. All final contacts must be documented in participant study records.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

A sub-group of the Protocol Team, including the MTN Safety Physicians, the MTN PI, MTN-004 Protocol Chair, MTN Protocol Specialist, Statistical Data Management Center (SDMC) Clinical Affairs Research Nurse, SDMC Project Manager, both Site PIs, FHI Protocol Coordinator, DAIDS and NICHD Medical Officers, and DAIDS Clinical Operations Study Coordinator, will serve as the Protocol Safety Review Team (PSRT). Close cooperation between the PSRT and other study team members will be necessary to monitor participant safety and respond to occurrences of toxicity in a timely manner.

8.2 Clinical Data Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are the first layer of this tiered system and are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise. Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC Clinical Affairs staff, the PSRT, and study sponsors. Additional special reviews may also be conducted as dictated by the occurrence of certain events.

All EAE reports submitted to the DAIDS Safety Office will be synchronously sent by the sites to the DAIDS Medical Officer, NICHD Medical Officer, SDMC Clinical Affairs Research Nurse, and the Protocol Chair for review. The SDMC Clinical Affairs staff review AEs, events requiring expedited reporting to DAIDS, and events that meet safety pause criteria.

During the active product use phase of the trial, the PSRT will review clinical and laboratory safety reports (blinded to treatment assignment) and conduct calls every two weeks, or as needed, to review the data as appropriate. The content, format and frequency of these reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to these routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to the MTN representing expertise in the fields of microbicides, biostatistics, and medical ethics may be invited to join the PSRT safety review.

After the product use and the final safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the MTN-004 PSRT.

Decisions regarding permanent discontinuation of study gel in individual participants will be made by the PSRT based on careful review of all relevant data and may involve sponsor consultation with the US Food and Drug Administration (FDA).

Accrual and overall study product use for all participants will be suspended for a data safety review by the PSRT if any two women enrolled in the study experience the same safety or toxicity endpoint, defined as:

1. Having at least one grade 3 or higher adverse experience during follow up judged by the investigator to be definitely, probably, or possibly related to the study gel or applicator, or:
2. Having at least one Grade 3 or higher macroscopic finding or other clinical evidence (excluding findings observed by colposcopy only) of damage during follow up (judged not to be due to pathogen or iatrogenic trauma) to the vulvar and/or vaginal deep epithelium and/or

cervical mucosa including ulceration and other lesions, severe global erythema, and/or severe global edema judged definitely, probably, or possibly related to the study gel or applicator.

Any additional two women with the same safety or toxicity event will be referred to the PSRT for discussion. The PSRT may decide to invoke an additional pause. If the PSRT pauses overall study product use and then lifts the pause following a safety review, participants in active follow-up at the time of the pause will discontinue further product use. Such participants will continue to be followed up through study exit for safety follow-up. Adverse events assessed as probably not related, not related, or pending will not be considered when determining whether or not a safety pause shall occur. A decision to stop the trial may be recommended by a quorum of the PSRT at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed. The quorum will consist of the DAIDS Medical Officer, a NICHD Medical Officer, and one of the MTN safety physicians.

In the unlikely event that the protocol team has serious safety concerns that lead to a decision to permanently discontinue study gel for all participants and stop accrual into the study, the protocol team will request an unblinded review of the data by the NIAID Data and Safety Monitoring Board (DSMB) before recommending that the study be stopped. Members of the NIAID DSMB will be independent investigators with no financial interest in the outcomes of this study. If at any time, a decision is made to discontinue study gel in all participants, Starpharma Pty Ltd after consultation with the DAIDS and the protocol team will inform the US FDA. The Site PI's will notify the responsible IRBs expeditiously.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition will be applied to both treatment arms. The term "investigational product" for this study refers to VivaGel[®], VivaGel[®] placebo, and HEC gel as well as the study gel delivery applicators.

Study participants will be provided a 24-hour telephone number and instructed to contact the study clinician to report any AEs they may experience, except for life-threatening events, for which they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek medical care where the study clinician is based, and to request that the clinician be paged or otherwise contacted upon their arrival. With appropriate permission of the participant, whenever possible records from all non-study medical providers related to

AEs will be obtained and required data elements will be recorded on study case report forms. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

Participants who are found to have clinical findings or microscopic evidence consistent with bacterial vaginosis or vaginal candidiasis or both, but who do not report associated symptoms, will not have those diagnoses (asymptomatic bacterial vaginosis, asymptomatic vaginal candidiasis) reported as adverse events.

Participants who develop any pelvic exam abnormality, excluding findings observed by colposcopy only, will be followed until the AE resolves or stabilizes. Participants will be encouraged to report to the study clinician any problems experienced by their male partners that might be potentially related to study product. The study clinician will suggest follow up care or a referral for such care if deemed appropriate. Study site staff will document on study CRFs all AEs reported by or observed in enrolled study participants or their partners from the time of their first dose of study gel through the Three-Week Clinic Visit or early termination, regardless of severity and presumed relationship to study gel or applicators. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004, Addendum 1 (The Female Genital Toxicity-Grading Table for Use in Microbicide Studies) will be the primary tool for grading adverse events for this protocol, with the exception of asymptomatic bacterial vaginosis which will not be a reportable AE, as noted above. Adverse events not included in that table will be graded by the DAIDS AE Grading Table Version 1.0, Dec 2004. In cases where an AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized. These tables are available at: <http://rcc.tech-res.com/eae.htm>.

8.3.2 AE Severity/Intensity

The severity (intensity) grades that will be used for this study are defined in the DAIDS AE Grading Table Version 1.0, Dec 2004 and Addendum 1 to the table. These tables are available at: <http://rcc.tech-res.com/eae.htm>.

8.3.3 Serious Adverse Event

Serious Adverse Event (SAE) will be defined per 21 CFR 312.32 guidelines. A serious adverse event is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Study sites will report any SAEs to Starpharma within 24 hours of their knowledge of the SAE. SAEs will be reported to the FDA by Starpharma Pty Ltd. SAE reports sent to the FDA will be simultaneously sent by Starpharma Pty Ltd to the DAIDS and NICHD Medical Officers.

8.3.4 Adverse Event Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. Degrees of relatedness will be categorized as one of the following.

Definitely related: adverse event and administration of study agent are related in time, and a direct association can be demonstrated with the study agent.

Probably related: adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by the study agent than by other causes.

Possibly related: adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than the study agent.

Probably not related: a potential relationship between administration of study agent and adverse event could exist, but is unlikely, and the adverse event is most likely explained by causes other than the study agent.

Not related: the adverse event is clearly explained by another cause unrelated to administration of the study agent. Reportable events must have documentation to support the determination of “not related”.

8.4 Expedited Adverse Event Reporting Requirements

This section outlines Expedited Adverse Event (EAE) reporting requirements for MTN-004. Study sites will receive training on EAE reporting prior to the onset of study enrollment.

8.4.1 Expedited Adverse Event Reporting to DAIDS and Starpharma Pty Ltd

The EAE reporting requirements and definitions for this study and the methods for expedited reporting of AEs to the DAIDS RCC Safety Office are defined in “The Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual) **dated May 6, 2004**. The DAIDS EAE Manual is available on the RCC website: <http://rcc.tech-res-intl.com/>. The DAIDS EAE Manual is also available in the MTN-004 Study Operations Manual.

AEs reported on an expedited basis must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) available on the RCC website: <http://rcc.tech-res-intl.com/>.

EAEs must be faxed to DAIDS and Starpharma Pty Ltd as outlined in the SSP. Medical Officers from both DAIDS and NICHD are also to receive timely and synchronous communications of any adverse event reported to the RCC from the sites. They will engage in any necessary dialogue or consultation with each other in order to render a decision. If agreement cannot be reached, the ultimate decision will be rendered by the Medical Officer from the MTN’s primary sponsoring institute (NIAID/DAIDS) (or the individual designated to cover for them in their absence).

8.4.2 EAE Reporting Requirements for this Study

EAE Reporting Level

This study uses the **Intensive Level** of expedited AE reporting as defined in the DAIDS EAE Manual.

Study Agents for Expedited Reporting to DAIDS

The study agents that must be considered in determining relationships of AEs requiring expedited reporting to DAIDS are: study agent delivery applicator, VivaGel[®], VivaGel[®] placebo, and HEC gel.

Study Agents for Expedited Reporting to Starpharma Pty Ltd

The study agents that must be considered in determining relationships of AEs requiring expedited reporting to Starpharma Pty Ltd are: study agent delivery applicator, VivaGel[®], VivaGel[®] placebo, and HEC gel.

Grading Severity of Events

The DAIDS AE Grading Table, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies) will be the primary tool for grading adverse events for this protocol, with the exception of asymptomatic bacterial vaginosis and asymptomatic candidiasis which will not be a reportable AE as noted above. AEs not included in that table will be graded by the DAIDS AE Grading Table Version 1.0, Dec 2004. In cases where an AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized. These tables are available at: <http://rcc.tech-res.com/eae.htm>.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December, 2004 is available on the RCC website at <http://rcc.tech-res.com/eae.htm>. The DAIDS AE Grading Table is also available in the MTN-004 Study Specific Procedures (SSP) Manual.

EAE Reporting Periods

AEs must be reported on an expedited basis at the **Intensive Level** during the Protocol-defined EAE Reporting Period, which is:

The entire study duration for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).

After the end of the Protocol-defined EAE Reporting Period stated above, sites must report serious, unexpected, clinical suspected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

8.5 Local Regulatory Requirements

Site investigators will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. This reporting will include site IRB-mandated reporting of AEs, SAEs, and other relevant safety information.

9 CLINICAL MANAGEMENT

This section summarizes guidelines for clinical management for individual participants in the case of unplanned health events, including product toxicity, other disease events, and pregnancy.

9.1 Toxicity Management

Based on results from the first Phase 1 study of VivaGel[®], toxicity in study participants is not expected in this trial. In response to AEs reported by study participants and/or observed upon exam by study staff, the study site principal investigator or designee will recommend either continuation or withholding study gel use consistent with the criteria in Appendix II.

Study gel use also will be withheld or discontinued in the event of an Expedited Adverse Event (EAE) that is judged by the site principal investigator or designee to be definitely, probably, possibly, or probably not related to the study gel or applicator. Unless the participant withdraws her consent, she will remain in the study to complete the safety

evaluations (unless clinically contraindicated) according to Appendix I, and/or as specified in Appendix II.

9.2 Other Disease Events

Management of confirmed sexually transmitted infections/sexually transmitted diseases, commonly referred to as STIs or STDs, and other forms of vaginitis and cervicitis will be in accordance with CDC Guidelines.

9.3 Pregnancy

All participants will be instructed to report pregnancies to site investigator or to the study staff who will in turn report to the site investigator; the site investigator will inform PSRT. The site investigator will counsel the participant and discuss possible risks if the pregnancy is continued according to site-specific SOPs.

Participants who are found to be pregnant during the study period will continue to be followed for safety reasons until the end of their study participation (study exit visit). Participants who are pregnant at the time of the study exit visit will continue to be followed until the pregnancy outcome is ascertained or it is determined that, after multiple attempts, pregnancy outcome cannot be ascertained. The site PIs will attempt to ascertain the pregnancy outcome, and pregnancy outcomes will be reported to SCHARP on the Pregnancy Outcome form. Any pregnancies will be reported to the PSRT. Pregnancies with abnormal outcomes will be reported according to all applicable EAE guidelines listed in Section 8.4.

Sites will provide a single brand of lubricated (non-N-9 or -spermicide containing), male, latex condoms for the purpose of this study, and facilitate participants' access to all contraceptive methods. In the event of pregnancy, sites will counsel participants and will facilitate access to services, according to the site-specific SOPs. However, sites will not be responsible for paying for pregnancy-related care. Participants who become pregnant during the course of the study will discontinue study gel use while they are pregnant, but will not routinely be withdrawn from the study. Rather, if the participant does not withdraw her consent, every effort will be made to complete the safety evaluations according to Appendix I.

For participants who become pregnant, all protocol-specified procedures will continue except:

- Administration of study gel (The site staff will make every effort to recover any unused study product once pregnancy is diagnosed.)

9.4 Criteria for Discontinuation of Study Product, and Discontinuation of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The principal investigators may withdraw participants to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. The investigators may withdraw a participant from the study if any condition in the opinion of the investigator would impose a health risk to the participant or interfere with the evaluation of the study product. Participants withdrawn for safety reasons by the investigator will continue to be followed with the protocol-determined schedule of follow-up visits, unless consent is withdrawn.

Discontinuation of study participation will occur only if certain conditions below are met. These conditions are related to safety as well as impact on reaching planned study endpoints.

9.4.1 Criteria for Permanent Study Product Discontinuation for an Individual Participant

The criteria for permanent discontinuation of further study product use for an individual participant are:

- Signs or symptoms of STI(s)/RTI(s) requiring treatment according to the judgment of the investigator
- Study product-related toxicity (see Section 9.1)
- Pregnancy or breastfeeding
- Completion of regimen as defined in the protocol
- Request by participant to terminate treatment
- Clinical reasons determined by the physician

The participant will continue to be followed with the participant's permission if study product is discontinued. No subsequent modifications to the visit schedule and duration of continued follow-up will be made, except no study product will be administered.

9.4.2 Criteria for Premature Study Discontinuation for an Individual Participant

Safety or other considerations may make it appropriate to have a participant prematurely discontinue the study. The criteria for premature discontinuation from the study for an individual participant are:

- Lost to follow-up as evidenced by failure by the participant to attend two consecutive clinic visits
- Participant repeatedly non-compliant with study treatment as prescribed (e.g. non-compliant with instructions for dosage, route, regimen, or male condom use)
- Request by participant to withdraw

- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant

10 STATISTICAL CONSIDERATIONS

10.1 Overview and General Design

This is a two site, Phase I, double blind, randomized, controlled comparison with 14 days of twice daily exposure to VivaGel[®], VivaGel[®] placebo, or HEC gel, and follow-up among HIV-uninfected sexually active women.

10.2 Study Endpoints

10.2.1 Primary Endpoint

Consistent with the primary study objective to assess the safety of study drug when administered twice daily for 14 consecutive days on vulvar and cervicovaginal mucosa, the following primary endpoints will be assessed:

- Abnormal genital symptoms judged by the Investigator to be possibly, probably, or definitely related to product use;
- Abnormal pelvic exam findings, (excluding findings observed by colposcopy only), judged by the Investigator to be possibly, probably, or definitely related to product use;
- Grade 3 or higher laboratory values (as defined by the DAIDS Toxicity Tables) for hematology, liver function, creatinine level and coagulation judged by the Investigator to be possibly, probably, or definitely related to product use;
- Adverse experiences judged by the Investigator to be possibly, probably, or definitely related to product use.

10.2.2 Secondary Endpoints

Consistent with the secondary study objectives to assess adherence to, and acceptability of, a short-term regimen of VivaGel[®], and to assess the effect of this regimen on vaginal microflora, the following endpoints will be assessed:

- The proportion of participants who report via adherence questionnaire that they were adherent to the product use regimen, with adherence defined as the application of at least 80% of the expected number of doses of study product over the two weeks of product use;

- The proportion of participants who at their Two-Week Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during sexual intercourse in the future;
- Reported positive and negative aspects of using study product;
- Changes in vaginal flora.

10.2.3 Exploratory Endpoints

- Changes in cervical cytokine, innate immune factor (secretory leukocyte protease inhibitor (SLPI) and lactoferrin) expression, and functional activity (antiviral and antibacterial) in cervicovaginal secretions
- Detection of SPL7013 in blood samples at Day 0 and Two-Week Clinic Visit (Target Day 14)
- To assess the effects of VivaGel[®] on colposcopic findings

Changes within each arm and between arms will be reported.

10.3 Study Hypothesis

MTN-004 hypothesizes that VivaGel[®] will be safe, well-tolerated and acceptable for twice daily vaginal application among healthy sexually active young women.

10.4 Sample Size

The primary aim of the study is to assess the local and systemic safety of vaginal application of VivaGel[®] versus placebo gel among HIV uninfected women. The proposed total sample size is approximately n=61 evaluable participants with approximately 36 included in comparisons between VivaGel[®] and the HEC Gel (18 participants in each of the 2 arms), and approximately 43 included in comparisons between VivaGel[®], and VivaGel[®] placebo (18 participants in each of the 2 arms plus 7 previously enrolled). This sample size is based upon the size of similar Phase 1 studies of topical microbicide products. Additional participants may enroll in the study, at the discretion of the protocol team, to replace currently enrolled participants who are non-adherent to the study product and/or the study visit schedule. Finally, if for some reason a site experiences difficulty reaching its accrual target, consideration will be given to shifting enrollment “slots” to the other site, with prior approval of the Protocol Chair.

As a means to characterize the statistical properties of this study, the following table presents the probability of observing zero, at least one, and two or more safety endpoints among the minimum sample size of 18 women using VivaGel[®] for various “true” event rates:

Table 17: Analysis of Adverse Event Frequency with n = 18

Event Rate	P (0 events n=18)	P (≥ 1 event n=18)	P (≥ 2 events n=18)
1%	0.83	0.17	0.01
5%	0.40	0.60	0.23
10%	0.15	0.85	0.55
15%	0.05	0.95	0.78
25%	<0.01	>0.99	0.96
35%	<0.01	>0.99	>0.99
45%	<0.01	>0.99	>0.99

For example, if the true rate of a given endpoint is five percent, the probability that the endpoint will be observed in at least one of the (minimum of) 18 women exposed to VivaGel[®] is 0.60.

The actual number of women using VivaGel[®] who will be available for analysis is unknown, but is likely to be approximately 21. Given this, the table below presents the probability of observing zero, at least one, and two or more safety endpoints assuming 21 women were randomized to VivaGel[®] for various “true” event rates:

Table 18: Analysis of Adverse Event Frequency with n = 21

Event Rate	P (0 events n=21)	P (≥ 1 event n=21)	P (≥ 2 events n=21)
1%	0.81	0.19	0.02
5%	0.34	0.66	0.28
10%	0.11	0.89	0.64
15%	0.03	0.97	0.84
25%	<0.01	>0.99	0.98
35%	<0.01	>0.99	>0.99
45%	<0.01	>0.99	>0.99

10.5 Randomization Procedures

Women will be randomized at a 1:1:1 ratio to one of the three arms. Randomization will be stratified by site to ensure balanced assignment to each product (VivaGel[®], VivaGel[®] placebo, or HEC gel) within each site. The randomization scheme will be generated and maintained by the SDMC. The SDMC will provide each study site with one set of randomization envelopes to be stored and used in the study clinic. Clinic staff will assign these envelopes in sequential order, by envelope number, to eligible participants. Additional envelopes will be provided to each site for the purpose of enrolling >18 participants per site if non-adherent participants need to be replaced or if enrollment “slots” need to be shifted from one site to another.

Assignment of the randomization envelope is considered the effective act of participant enrollment/randomization. Clinic staff will prepare a written prescription contained within the envelope that, among other things, documents the randomization envelope number and randomization code indicating the product (VivaGel[®], VivaGel[®] placebo, or

HEC gel) to which the participant was assigned. Multiple codes will be utilized to conceal and protect the randomization assignments in this study. Clinic staff will store assigned randomization envelopes and copies of the study prescription in participants' study charts.

10.6 Justification for Placebo Gels

Inclusion of placebo gels in this safety trial will enable investigators to examine the incidence of adverse events in the presence of the study product containing SPL7013 in comparison to those occurring in the presence of the two different placebo gels (one of which is the same formulation as VivaGel[®], but containing no SPL7013, and one of which is a placebo gel that has been used in several placebo controlled microbicide trials) that have been shown to have good safety profiles and low likelihoods of inducing mucosal damage.

10.7 Blinding

Study staff and participants will be blinded to the random assignments of all study participants. All study gels will be supplied in identical, single-use applicators packaged in individual wrappers. Blinding will be maintained until all data are entered into the study database, all study endpoint data and other data included in the final analysis have been cleaned and verified, and the data are ready for final analysis. This will be explained to participants as part of the study.

10.8 Maintenance of Trial Randomization Codes

Trial randomization codes will be maintained by unblinded staff at the SDMC. There are no circumstances under which it is expected that unblinding to blinded study staff or participants will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants.

As described in Section 9.4, in the event that an Investigator is concerned that a participant might be put at an undue risk by continuing product use, the Investigator may discontinue use by this participant; however, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow up and/or treatment. If an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator will notify the PSRT to consider and rule upon the request.

10.9 Participant Accrual and Follow-Up

Based on previous studies of vaginal products with similar eligibility requirements, the accrual of eligible participants with normal reproductive tracts is expected to require the screening of approximately 160 volunteers. The target for retention will be 95% of enrolled participants over the 21-day follow-up period. Therefore, it is anticipated that

approximately 64 women will be enrolled in the study. Accrual is anticipated to take approximately 9 months. Monthly accrual targets will be available in the SSP.

10.10 Data and Safety Monitoring and Analysis

10.10.1 Study Monitoring Committee (SMC)

In addition to the safety monitoring done by the PSRT (described in section 8.1), the MTN SDMC will prepare study progress reports and reports of AEs experienced by study participants (blinded to treatment assignment) for review by the MTN Study Monitoring Committee (SMC). The SMC will conduct interim reviews of study progress (blinded to treatment assignment), including rates of participant accrual, retention, rates of adherence to study gel use, and product safety. These reviews will take place approximately every 90 days, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

10.10.2 Data Analysis

For analyses comparing VivaGel[®] to the VivaGel[®] placebo, data from approximately 43 women will be included (18 participants in each of the 2 arms plus 7 previously enrolled) whereas for analyses comparing VivaGel[®] to the HEC gel, data from approximately 36 women will be included (18 participants per arm). All references to “control gel” below apply to 1) the VivaGel[®] placebo in analyses comparing VivaGel[®] to the VivaGel[®] placebo and, 2) the HEC gel in analyses comparing VivaGel[®] to the HEC gel.

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Within-treatment group assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar’s test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). When use of formal testing to assess differences between users of the control gel and users of VivaGel[®] is required, the following methods will be used: for binomial response variables, chi-square tests and logistic regression; for continuous variables, t-tests and linear regression or nonparametric methods if data are non-Normal.

To assess the adequacy of the randomization, control gel and VivaGel[®] participants will be compared for baseline characteristics including demographics, pelvic examination, and laboratory measurements using descriptive statistics. Due to the small sample size, formal comparisons will not be done.

Primary Analyses

The primary aim of the study is to assess the toxicity of VivaGel[®] on vulvar and cervicovaginal mucosa. All visits in which a woman has been exposed to the study product will be included in the primary analysis of safety. Secondary intent to treat analyses may also be performed. To assess safety, the number and the percentages of participants experiencing at least one AE, and the number and percentage experiencing each specific AE will be tabulated by study arm. Each participant will contribute once in each category (i.e. only for highest severity AE for each participant) for the calculation of event rates. The number and percentage of participants experiencing each type of AE (including AEs leading to study discontinuation) will be tabulated by severity and relationship to treatment for each treatment group. AEs that lead to study product discontinuation will be listed in a separate data listing. Overall summaries by treatment group include the number and percentage of participants experiencing: (1) any experience; (2) any moderate, severe, or life-threatening experience. The number and percentage of participants with an AE judged possibly, probably or definitely related to study treatment will be summarized for each treatment group. Grade 3 or higher toxicity for hematology, coagulation function, liver function, or creatinine level is also a primary endpoint. Baseline and Two-Week visit laboratory measures will be summarized and the change in function, defined by the difference between Two-Week and baseline measurements, will be evaluated by treatment group.

Secondary Analyses

One secondary study objective is to assess adherence to a short-term regimen of VivaGel[®]. To assess adherence, the proportion of participants who applied 80% of the expected number of doses of study product over the two weeks of product use will be calculated by treatment arm. All enrolled women will be included in this analysis.

An additional secondary study objective is to evaluate aspects of product acceptability. To evaluate acceptability, the proportion of participants who at their Two-Week Follow-up Visits report via acceptability questionnaire that they would be extremely likely to use the candidate microbicide during sexual intercourse in the future will be calculated by treatment arm. In addition, positive and negative aspects of using the study drug will be listed in order of frequency. All enrolled women with a Two-Week follow-up visit will be included in these analyses.

The final secondary study objective is to assess the effect of a twice-daily short-term regimen of VivaGel[®] on the vaginal microflora of sexually active HIV-uninfected women. To assess the effect of SPL7013 on vaginal flora, clinically significant changes in vaginal flora will be evaluated by the Nugent score with shift tables from baseline (Enrollment) to follow-up visits. The Nugent score is graded 1 to 10 as follows:

1. Normal, 0 to 3
2. Intermediate, 4 to 6
3. BV, 7-10

Any shift from normal at baseline to intermediate or BV at a follow-up visit, or intermediate at baseline to BV at a follow-up visit, will be considered a clinically meaningful change in vaginal flora. Changes within each treatment arm will be reported. In addition, differences between the treatment groups in the distribution of Nugent scores at follow-up visits will be formally tested.

In addition to looking at shifts in the Nugent score, within treatment arm descriptions, and between treatment arm comparisons, will be done to assess clinically meaningful changes in quantitative measures of vaginal flora (defined by more than ≥ 1 log change in dominant members of the microflora, including *Lactobacillus* (H_2O_2 positive and negative strains), anaerobic gram negative rods, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, *Candida* species, Group B *Streptococcus*, and *Enterococcus* species) and to assess differences in the quantitative levels of these flora between treatment arms during follow-up.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study case report forms will be developed by the SDMC. Quality control reports and queries routinely will be generated and distributed to the study sites for verification and resolution.

11.2 Source Documents and Access to Source Data/Documents

The investigator will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, the investigator will retain all study records indefinitely. Study records will not be destroyed prior to receiving approval for record destruction from DAIDS and Starpharma. Applicable records include source documents, site registration documents and reports, correspondence, informed consent forms, and notations of all contacts with the participant.

11.3 Quality Control and Quality Assurance

Dr. Sharon Hillier, who completed a training program in clinical and public health microbiology certified by the American Board of Medical Board of Microbiology, directs the Site Support and Diagnostic Training Core in the MTN Network Laboratory at Magee-Womens Research Institute. This laboratory is Clinical Laboratory Improvement

Amendments (CLIA)-inspected and maintains its own CLIA license. Thus, all testing done in this research laboratory is performed with the same level of quality control as required in a licensed clinical laboratory.

Dr. John Mellors directs the Virology Core in the MTN Network Laboratory at the University of Pittsburgh School Of Medicine. This laboratory is CLIA-certified and has consistently met proficiency standards for HIV-1 RNA testing established by the DAIDS-sponsored Virology Quality Assurance program. All HIV-1 endpoint confirmations will be done in this laboratory.

See Section 12 for site monitoring plan.

11.4 Study Coordination

Starpharma Pty Ltd holds the IND application for this study (#62,482). Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS, NICHD, and Starpharma Pty Ltd. Study site staff will be provided with the DAIDS SOPs for Source Documentation and Essential Documents, the Manual for Expedited Reporting of Adverse Events to DAIDS, and the DAIDS AE Grading Table. Training and written instructions outlining management and reporting, study gel dispensing, product accountability, and other study operations will be provided by Family Health International, the Statistical Center for HIV/AIDS Research & Prevention (SCHARP), and the MTN Network Laboratory. The final study report will be consistent with both DAIDS and ICH E3 guidelines.

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by Westat (Rockville, MD). On-site study monitoring will be performed in accordance with DAIDS policies. Site monitoring visits will be conducted to assess compliance with Health and Human Services (HHS) Regulations 45 CFR Part 46 and 21 CFR Parts 50, 56, and 312. Study monitors will visit the site to:

- Verify compliance with human subjects and other research regulations and guidelines, including confidentiality procedures, informed consent process, and regulatory documentation
- Assess adherence to the study protocol, study-specific procedures manual, and local counseling practices, including compliance related to study product management and pharmacy-related procedures
- Confirm the quality and accuracy of information collected at the study site and entered into the study database, including the validation of data reported on case report and DataFax forms

- Assess the resolution of any past or ongoing issues identified at previous monitoring visits

A minimum of three monitoring visits per site will occur for this study, including a visit shortly after study initiation, one at the perceived midpoint for enrollment, and a third for study closeout.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, MTN NL, Family Health International, Statistical Center for HIV/AIDS Research & Prevention, NIAID, NICHD, Starpharma Pty Ltd, FDA, and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

The investigators will make efforts to minimize risks of this new product to human participants. Volunteers will take part in a thorough informed consent process throughout their participation in the study. Before beginning the study, the investigators will have obtained IRB approval and the protocol will have been submitted to the FDA. The investigators will permit audits by the NIH, Starpharma Pty Ltd or the FDA or any of their appointed agents.

13.1 Institutional Review Boards

Each participating institution is responsible for assuring that this protocol and the associated informed consent documents and study-related documents are reviewed by an Ethics Committee (EC) or Institutional Review Board (IRB) prior to implementation of the protocol. Any amendments to the protocol, informed consents, or other study-related documents must be approved by the EC/IRB, NICHD, and DAIDS prior to implementation.

13.2 Protocol Registration

Each participating institution will complete protocol registration with the NICHD via Westat. After study sites have received final approval from their local IRB, they must submit protocol registration materials to the Data and Operations Center (DOC) at Westat in accordance with ATN requirements. When the DOC has received all required registration materials, the DOC will approve the site's protocol registration and notify the site that it may begin protocol enrollment. Protocol registration must occur before the site can enroll any participants into the study.

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair, NIAID Medical Officer, and NICHD Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s), and where necessary by Starpharma to the FDA, prior to implementing the amendment.

Following ethical review and approval, study sites will submit required administrative documentation to the ATN DOC, Westat. NICHD has delegated responsibility for review and approval of protocol-specific regulatory documentation to Westat. Included in this step will be MTN CORE review of each site-specific study informed consent form.

13.3 Risk/Benefit Statement

Risks

Before testing in humans VivaGel[®] and the active ingredient were tested in animals. VivaGel[®] was well tolerated in a number of animal studies using rats, mice, guinea pigs, dogs, rabbits and monkeys. At one laboratory, some rabbits died when they received VivaGel[®] in the vagina at various doses similar to those that will be used in this study. However, this effect was not seen in other studies when VivaGel[®] was applied to the vaginas of female rats, dogs, monkeys, and in other studies in rabbits at one other laboratory, in which no rabbits died. Further investigation indicated that the deaths of the rabbits were likely to be related to the procedure used at that laboratory to administer the VivaGel[®] to the vagina. Rabbits have a place in the vaginal wall where blood vessels are concentrated. It was concluded that damage was caused to that area of the vaginal wall by the dosing procedure, which in turn caused bleeding. Humans, monkeys and rats do not have this concentration of blood vessels in the vagina. It is considered that the effects seen in that rabbit study do not represent a risk to the participants in this or any other clinical trial of VivaGel[®]. However, the researchers could not determine the exact cause of death in these rabbits.

It is not expected that this trial will expose participants to unreasonable risk. The intervention used in this study is unlikely to cause uncomfortable side effects. An unpublished clinical study suggests a low incidence of side effects, both in the VivaGel[®] and placebo gel groups.

In the first clinical study of VivaGel[®] (Starpharma Protocol Number SPL7013-001), volunteers reported the following adverse events that were deemed at least possibly related to study product: vaginal pruritus, vaginal discharge (including product leakage), abdominal discomfort or pain, and dysuria. A rare but potentially life-threatening risk of exposure to either study agent would be anaphylaxis (has not yet been reported for either VivaGel[®] or placebo gel). Use of a vaginal applicator may cause discomfort, and rarely, vaginal or cervical injury. Colposcopy may also cause mild discomfort secondary to speculum placement in the vagina for the 10-15 minute examination. Collection of cervical cells by Cytobrush[®] may cause discomfort or spotting during specimen

collection. Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection.

Male sexual partners will be protected from potential risks of study drug exposure by the use of condoms throughout the study.

Disclosure of STI status may cause sadness or depression in volunteers. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial, as well as social isolation. Participation in clinical research includes the risks of loss of confidentiality and discomfort with personal nature of questions.

Benefits

Participation in this Phase 1 trial likely will have no direct benefit to volunteers other than access to screening for STIs and appropriate referral if STIs are diagnosed. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities in serology, blood count, coagulation, liver or kidney function tests. Pap smear and colposcopy may offer the opportunity for early detection of a cervical and/or vaginal abnormality with expedient referral if an abnormality is detected. Lastly, the participant may appreciate the opportunity to contribute to the body of knowledge in the field of microbicide research. However, there is no guarantee that volunteers will receive any of these benefits.

13.4 Informed Consent Process

Written informed consent will be obtained from all potential study participants prior to the initiation of any study-related procedures. In obtaining and documenting informed consent, the investigators will comply with applicable local and domestic regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the trial, site investigators will have the IRB/EC's written approval/favorable opinion of the protocol, informed consent forms, and any other study-related information to be provided to participants. This study does not plan to enroll children under 18 or illiterate individuals. All study related materials including the informed consent forms will be available in English and Spanish as required by each study site.

The informed consent process will give individuals all of the relevant information they need in order to decide whether to participate, or to continue participation, in this study. Potential research participants will be permitted to ask questions and to exchange information freely with the study investigators. Only listed study investigators may obtain informed consent from potential study participants. The investigators will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

13.5 Participant Confidentiality

Members of the study staff sites are all trained in patient confidentiality for their participation in the ATN. The only sites at which this study will be performed are both ATN Trials Units (ATU). The log of study participant names and other protected health information will be kept in a double-locked area. All computer information about study volunteers will be kept on a computer with log-on passwords. Laboratory specimens are labeled with study numbers and date, and are delivered or shipped by study staff. The study sites' data management and clinical staff are the only personnel with access to the protected health information of study volunteers. Each member of the staff has log-on identification and password, logs off before leaving a computer screen unattended, and closes their office door when out of the office. All research records will be kept indefinitely following closure of this study.

To further protect the privacy of the study participants, the ATN has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). With this Certificate in place, the ATN researchers cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study participant.

13.6 Special Populations

This section outlines considerations made for the inclusion or exclusion of special populations in this study.

13.6.1 Pregnant Women

Pregnancy is an exclusion criterion because there are no current recommendations for the use of VivaGel[®] during pregnancy. A urine pregnancy test will be performed on all women at all clinic visits, and positive tests will be noted on the Eligibility Criteria form. During the informed consent process, women will be informed that VivaGel[®] is not known to prevent pregnancy and that the effect of VivaGel[®] on a developing human fetus is unknown. All potential participants will be required by the Eligibility Criteria for Screening and Enrollment to be currently using a reliable method of contraception, such as hormonal contraception (except vaginal ring), intrauterine device, or sterilization. Women who become pregnant during the study period following randomization and exposure to study product will discontinue product use but not be excluded from analysis.

13.6.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study will enroll women aged 18 to 24 who are able to give informed consent. This study meets “Justifications for Exclusion” criteria for younger children as set forth by the NIH. Specifically, “insufficient data are available in adults to judge potential risk in children” and “children should not be the initial group to be involved in research studies.

13.7 Incentives

Pending IRB approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Site-specific reimbursement amounts will be specified in the study informed consent forms.

13.8 Communicable Disease Reporting

Study staff will comply with all applicable local requirements to report communicable diseases including HIV identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

13.9 Access to HIV-Related Care

This section outlines study participants’ access to HIV-related care, including HIV counseling and testing, as well as care for participants identified as HIV-infected.

13.9.1 HIV Counseling and Testing

HIV pretest and post-test counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study. Participants must receive their HIV test results to take part in this study. The investigators do not expect a screening population at high risk for HIV infection. However, trained clinical staff will refer participants who are confirmed to be HIV-infected per the HIV Antibody Testing Algorithm in Appendix III to a physician for follow-up testing and care. Participants who have positive or indeterminate results will have standard post-test counseling as well as limited follow-up confirmatory testing provided by the study. Referral for additional counseling related to testing or diagnosis will occur if needed or requested by the participant.

13.9.2 Care for Participants Identified as HIV-Infected

Study staff will provide participants with their HIV test results in the context of post-test counseling. According to site SOPs, study staff will refer participants found to be HIV-infected to available sources of medical and psychological care, social support, and local research studies for HIV-infected women.

13.10 Study Discontinuation

This study may be discontinued at any time by NIAID, NICHD, the MTN, Starpharma, the US FDA, other government or regulatory authorities, or site IRBs.

14 PUBLICATION POLICY

DAIDS and MTN policies and a Memorandum of Agreement (MOA) between MTN and ATN, and a Clinical Trial Agreement (CTA) between Starpharma, NICHD and NIAID, will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the Investigator to the MTN Manuscript Review Committee, DAIDS, NICHD and Starpharma Pty Ltd, for review prior to submission.

APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	Screen 1	Screen 2	Enroll	Phone Call	1-Week Clinic Visit	2-Week Clinic Visit	3-Week Clinic Visit	Inter./Safety Visit
Target Day	≤30 Days		Day 0	Day 2	Day 7	Day 14	Day 21	PRN
Window Period	≤36 Days		Day 0	Day 2-4	Day 6 – 8	Day 13 – 15	Day 20 – 24	
Study Communications								
Informed Consent	X		X					
Assign Participant ID	X							
Eligibility Assessment	X	X	▲					
Collect Demographics	X							
HIV Pre- & Post-Test Counseling	X							
Screening Results (as available)	X	X	X					
Treatment or Referral	▲	▲	▲		▲	▲	▲	▲
Record/Update Medical and Menstrual History	X	X	X		X	X	X	X
Baseline Behavioral Questionnaire			X					
Record/Update Con. Meds.			X		X	X	X	▲
Record Adverse Events					X	X	X	▲
Vaginal Product History			X					
Acceptability Assessment						X		
Adherence Assessment					X	X		
Male Condom Counseling	X	X	X		X	X		▲
Record/Update Contacts	X	X	X		X	X	X	X
Schedule Next Visit	X	▲	X		X	X	▲	▲
Obtain Random Assignment			X					
Phone Assessment				X				
Study Burden Questionnaire							X	
Reimbursement	X	X	X		X	X	X	
Laboratory								
Qual. Urine Pregnancy Test	X	X	▲		X	X	X	X
Urinalysis	X		▲		▲	▲	▲	▲
Urine Culture & Sensitivity	▲		▲		▲	▲	▲	▲
CBC, Liver Function Panel, Creatinine Level, Coag. Panel	X		X		X	X	▲	▲
RPR (Syphilis)	X		▲		▲	▲	▲	▲
Confirmatory Tests for Syphilis	▲		▲		▲	▲	▲	▲
HIV Antibody Screen	X							▲
HIV Confirmatory Testing	▲							▲
SPL7013 Level			X			X		
Plasma Archive			X			X		
Vaginal pH	X		X		X	X	X	▲
Quantitative Vaginal Cultures			X		X	X	X	▲
Vaginal Wet Prep Slide	X		X		X	X	X	▲
Gram-Stained Vaginal Smears	X		X		X	X	X	▲
Cervical Swabs for Cytokines and Innate Factors			X		X	X	X	▲
Urine SDA for Gonorrhea & Chlamydia	X		▲					
Genprobe Aptima					▲	▲	▲	▲
Pap Smear of Cervix	X							▲
Herpes Culture	▲				▲	▲	▲	▲
Clinical								
Colposcopy			X		▲	X	▲	▲
Vital Signs	X		X		X	X	X	▲
Abdominal/Pelvic Exam	X		X		X	X	X	▲

X=protocol-defined procedure; ▲=performed as clinically indicated; Plasma archive will only apply if participant has signed the consent for Storage of Specimens

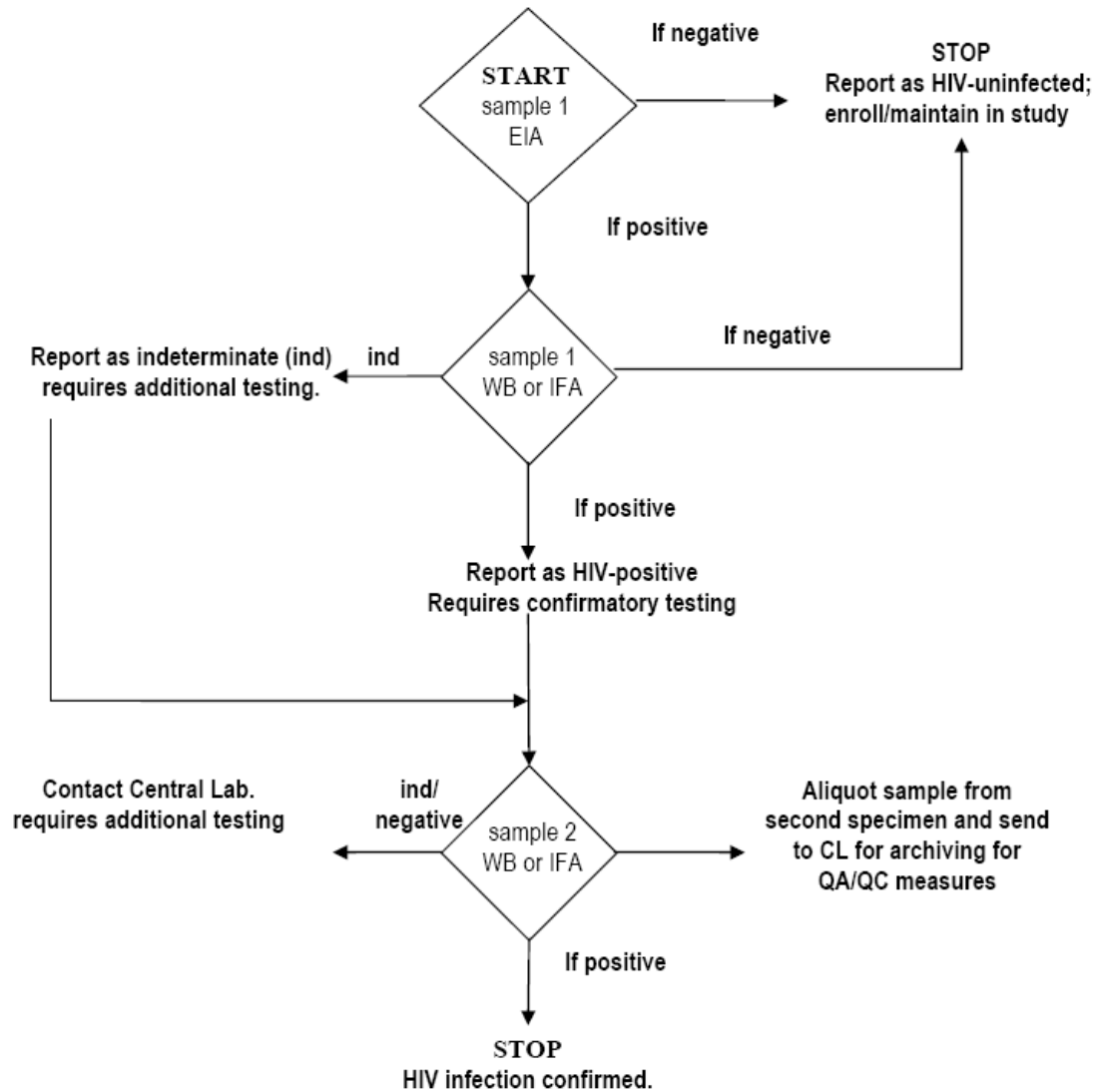
APPENDIX II: OUTCOMES, DIAGNOSTICS, AND FOLLOW-UP EVALUATIONS

CONDITION	PRODUCT USE	EVALUATION	FOLLOW-UP AND TREATMENT ACTION
Deep Epithelial Disruption (Ulceration) excluding findings observed by colposcopy only	Hold study gel (until evaluated)	Swab for herpes simplex culture. Perform syphilis serology (Herpes serology optional)	Re-evaluate in 48 - 72 hours and reinstate gel use if resolved. If the ulcer has become worse or not healed in 48 - 72 hours, follow the lesion per local standard of care. Ask participant to return in 7–10 days for follow up syphilis serology. If there is reoccurrence and there is no other etiology, then consider permanent discontinuation.
Superficial Epithelial Disruption (Abrasion/Peeling) excluding findings observed by colposcopy only	Continue	Naked eye evaluation with or without colposcopy	Re-evaluate by speculum examination in 48 - 72 hours. If condition is significantly worse, hold study gel. Otherwise continue gel use.
Localized erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface excluding findings observed by colposcopy only	Continue	Naked eye evaluation with or without colposcopy	If asymptomatic, re-evaluate at next regularly scheduled visit. If symptomatic, re-evaluate by speculum examination in 5 – 7 days. If worsened significantly, hold study gel use, until further evaluation is scheduled. Otherwise, continue gel use.
Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema excluding findings observed by colposcopy only	Hold study gel (until evaluated)	Naked eye evaluation with or without colposcopy	Re-evaluate in 48 - 72 hours and reinstate gel use if resolved. If there is reoccurrence and there is no other etiology, then consider permanent discontinuation.
Abnormal vaginal discharge	Hold study gel (until evaluated)	Perform wet mount for Candida vaginitis, trichomoniasis, and	Provide treatment and permanently discontinue gel use for all cases of trichomoniasis,

		BV	symptomatic Candida vaginitis, and symptomatic bacterial vaginosis. Gel use may be continued without treatment in the presence of asymptomatic Candida vaginitis and/or asymptomatic bacterial vaginosis.
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Unexpected genital bleeding	Continue (at clinician's discretion)	Naked eye evaluation with or without colposcopy	If determined to be due to deep epithelial disruption, refer to guidelines in this table. Otherwise continue gel use.
Presumed cervicitis (findings on exam such as mucopurulent cervical discharge)	Hold study gel (until evaluated)	Evaluate for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>	Provide treatment and permanently discontinue gel use for all cases of cervicitis.
Genital petechia(e) excluding findings observed by colposcopy only	Continue	Naked eye evaluation	No further evaluation or treatment required.
Genital ecchymosis excluding findings observed by colposcopy only	Continue	Naked eye evaluation with or without colposcopy.	No further evaluation or treatment required.
EAE that is judged by the site investigator or designee to be definitely, probably, possibly, or probably not related to the study gel or applicator	For Grades 1, 2, and 3 - Hold study gel (until evaluated) For Grade 4 – Permanent Discontinuation	Evaluate as according to current clinical practice at the site Not applicable	Provide treatment as clinically indicated, when resolved reinstate gel use at clinician's discretion Not applicable

APPENDIX III: HIV ANTIBODY TESTING ALGORITHM



Note: HIV positive results will only be reported to participants once the result is confirmed by Western Blot Testing. Once a participant's HIV status is confirmed, sites will follow site specific SOPs for notification to local agencies.

APPENDIX IV: MANUAL FOR EXPEDITED REPORTING OF ADVERSE EVENTS TO DAIDS

May 6, 2004

Table of Contents

1.0 PURPOSE OF MANUAL

- 1.1 Purpose
- 1.2 Scope.
- 1.3 Introduction

2.0 DESCRIBING AN ADVERSE EVENT BY SERIOUSNESS, SEVERITY, RELATIONSHIP TO STUDY AGENT, AND EXPECTEDNESS

- 2.1 Seriousness
- 2.2 Severity (Intensity)
- 2.3 Seriousness vs. Severity (Intensity) of Adverse Events and Reporting Criteria
- 2.4 Relationship to Study Agent
- 2.5 Expectedness (Expected vs. Unexpected)

3.0 ADVERSE EVENTS REQUIRING EXPEDITED REPORTING AND THE STUDY/TRIAL REPORTING PERIOD

- 3.1 Levels of Adverse Event Reporting
- 3.2 Additional Protocol-Required Expedited Reporting Requirements
- 3.3 Additional Adverse Events That Should Be Reported for Any Study/Trial
Requiring Expedited Reporting to DAIDS
- 3.4 Protocol-Defined Expedited Adverse Event Reporting Period

4.0 METHOD AND TIMEFRAME FOR EXPEDITED REPORTING OF INDIVIDUAL ADVERSE EVENTS

5.0 ADDITIONAL EXPEDITED REPORTING REQUIREMENTS

- 5.1 Follow-up Reporting of Adverse Events
- 5.2 Reporting Recurrent Adverse Events
- 5.3 Reporting Change in Severity of Adverse Events
- 5.4 Study Physician Assessment and Signature

6.0 APPENDICES

- 6.1 Appendix A: Definition of Terms
- 6.2 Appendix B: Contact Information for DAIDS Safety Office
- 6.3 Appendix C: Summary Chart for Expedited Reporting of Adverse Events to
DAIDS for Protocol-Specified Study Agents

1.0 PURPOSE OF MANUAL

1.1 Purpose

The purpose of this Manual is to describe the criteria and method for expedited reporting of certain serious and other reportable adverse events to the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), through the DAIDS Safety Office.

1.2 Scope

This Manual applies only to those clinical studies/trials requiring expedited reporting of adverse events to the DAIDS Safety Office as stated in the protocol. This Manual applies to all study agents specified in the protocol as requiring expedited reporting to DAIDS. Although not covered under this Manual, note that DAIDS may require MedWatch reporting (using e.g., Form FDA 3500A or CIOMS I Form) to the Food and Drug Administration (FDA) and/or DAIDS for some studies. MedWatch reporting may only be applied to studies/trials of US FDA-approved study agents. Any requirements for MedWatch reporting will be identified in the study/trial protocol.

1.3 Introduction

For adverse events requiring expedited reporting to DAIDS, sites must follow the general reporting requirements and procedures described in this Manual. In order to fully define the expedited adverse event reporting requirements that apply to an individual study/trial, the protocol will specify:

- One of three Levels of Adverse Event Reporting (Section 3.1) and any other adverse events to be reported on an expedited basis (Section 3.2).
- The duration of the protocol-defined expedited reporting period.
- The name or category of each study agent (US FDA-approved or investigational) that requires expedited reporting of adverse events to DAIDS. This may include study agents in addition to those provided by the study/trial.

2.0 DESCRIBING AN ADVERSE EVENT BY SERIOUSNESS, SEVERITY, RELATIONSHIP TO STUDY AGENT, AND EXPECTEDNESS

The criteria for expedited reporting of adverse events to the DAIDS Safety Office include the seriousness of the outcome of the event, the severity (intensity) of the event, its relationship to study agent, and (only for the Targeted Level) expectedness, i.e., whether the adverse event is expected or unexpected.

2.1 Seriousness

The first consideration for expedited reporting of adverse events to DAIDS is the seriousness of the outcome of the event. The April 1996 International Conference on Harmonisation (ICH) guidance, "Good Clinical Practice: Consolidated Guidance," (ICH E6) defined a serious adverse event (SAE) as "any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.”

“Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above” may also be considered to be serious (October 1994 ICH guidance (E2A), “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting”).

2.2 Severity (Intensity)

The second consideration for expedited reporting of adverse events to DAIDS is the severity (intensity) of the event. In order to maintain consistency among studies/trials and sites, DAIDS has developed a list of common clinical and laboratory adverse events and defined grade 1 – 5 severity parameters to generate the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences (also known as “the toxicity tables”). These tables are located on the DAIDS Safety Office website at <http://rcc.tech-resintl.com>. Unless stated otherwise in the protocol, study staff is required to use the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences to determine the intensity of adverse events in order to establish consistency in adverse event reporting to DAIDS. Specific protocols may include additional or modified criteria for grading adverse events that are not included in the current versions of the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences.

2.3 Seriousness vs. Severity (Intensity) of Adverse Events and Reporting Criteria

For expedited reporting to DAIDS, the term “severity” (or “intensity”) is described as the grade for a specific event, i.e., mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). This is *not* the same as “serious,” which is based on subject/event *outcome or action* criteria usually associated with events that pose a threat to a subject’s life or functioning (ICH E2A).

2.4 Relationship to Study Agent

The third consideration for expedited reporting of adverse events to DAIDS is the judgment of causal association (relationship) between an adverse event and the study agent. The protocol must specify by name or category each study agent (either approved or investigational) that requires expedited reporting of adverse events to DAIDS. The study physician makes the site’s final assessment of the causal association based upon the temporal relationship to administration of the study agent(s), the pharmacology of the study agent(s), and his/her clinical

judgment. The terms used in DAIDS studies/trials to assess relationship of an event to study agent are:

- **Definitely Related.** The adverse event and administration of study agent are related in time, and a direct association can be demonstrated.
- **Probably Related.** The adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by study agent than other causes.
- **Possibly Related.** The adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than study agent.
- **Probably Not Related.** A potential relationship between study agent and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the study agent.
- **Not Related.** The adverse event is clearly explained by another cause not related to the study agent.
- **Pending.** Pending may be used as a temporary relationship assessment only for death and only if data necessary to determine relationship to study agent are being collected. The site is required to submit a final assessment within 3 business days after reporting the death. If no final assessment is made within 3 business days after the date of submission, the event will be assessed as possibly related to study agent. Any additional information received at a later time, including an autopsy report, should be submitted as a Follow-up Report.

A **suspected adverse drug reaction (SADR)** is an adverse event that could potentially have a causal relationship to the study agent (definitely, probably, possibly, probably not related, or for deaths, pending).

2.5 Expectedness (Expected vs. Unexpected)

Expected refers to the perspective of events previously observed, *not* on the basis of what might be anticipated from the pharmacological properties of the study agent. (ICH E2A) Unexpected refers to events whose nature or severity (intensity) is not consistent with those included in the package insert/summary of study agents that have been approved by the US FDA or in the Investigator's Brochure. (ICH E2A)

3.0 ADVERSE EVENTS REQUIRING EXPEDITED REPORTING AND THE STUDY/TRIAL REPORTING PERIOD

3.1 Levels of Adverse Event Reporting

The protocol will specify one of three Levels of Adverse Event Reporting. The Level of Adverse Event Reporting chosen for expedited reporting is based primarily upon the degree of risk that may be associated with the study agent.

3.1.1 Standard Level

Report all adverse events following any exposure to study agent that:

- Result in death **regardless** of relationship to study agent.
- Are congenital anomalies, birth defects, or fetal losses **regardless** of relationship to study agent.
- Result in persistent or significant disabilities or incapacities **regardless** of relationship to study agent.
- Are a **suspected adverse drug reaction**, i.e., definitely, probably, possibly, and probably not related, to a study agent that requires or prolongs existing hospitalization, or requires intervention to prevent significant/permanent disability or death.
- Are life-threatening (including all Grade 4 adverse events) **suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent.

3.1.2 Intensive Level

In addition to all adverse events reported for the Standard Level, also report all Grade 3 suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent. (The Intensive Level includes reporting Grades 3 and 4 SADRs.)

3.1.3 Targeted Level

Use of the Targeted Level of reporting is limited to non-IND studies/trials of US FDA-approved agents and doses for approved indications and populations. Report **only** the following adverse events:

- All events that result in death **regardless of relationship** to study agent.
- All congenital anomalies, birth defects, or fetal losses **regardless of relationship** to study agent.
- All persistent or significant disability or incapacity **regardless of relationship** to study agent.
- **Unexpected* suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent, that require or prolong existing hospitalization, or require intervention to prevent death or significant/permanent disability.
- **Unexpected*** life-threatening clinical **suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent. **DO NOT report** Grade 4 laboratory values that are not associated with a life-threatening clinical event.

*Unexpected events are events whose nature or severity is not consistent with the package insert/summary of product characteristics for a US FDA-approved study agent.

3.2 Additional Protocol-Required Expedited Reporting Requirements

In addition to specifying one of the reporting levels above, a protocol may require other adverse events to be reported on an expedited basis. In this case, the protocol will explicitly state the additional adverse events to be reported to

DAIDS. For example, in rare instances a protocol may specify use of the Intensive Level and also require Grades 1 and 2 SADR to be reported, or a protocol may require reporting of a specific type of adverse event regardless of grade.

3.3 Additional Adverse Events That Should Be Reported for Any Study/Trial Requiring Expedited Reporting to DAIDS

In addition to the reporting requirements described above, sites should report any of the following adverse events on an expedited basis:

- Suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that **do not meet the protocol-required reporting criteria**, but the Investigator believes are of sufficient concern to be reported on an expedited basis to DAIDS. This includes adverse events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent a serious adverse event. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias or convulsions that do not result in hospitalization.
- Unexpected, serious suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that occur at any time **after the protocol-defined expedited reporting period** if the study staff become aware of its occurrence. These events include deaths, permanent disabilities, congenital anomalies, hospitalizations, and life-threatening clinical events. (Do not report Grade 4 laboratory values unless associated with a life-threatening clinical event.)
- Serious adverse events that are not related to a study agent, but could be associated with **study participation or procedure** (e.g., pulmonary embolism secondary to an intravenous catheter placed for study agent administration).

3.4 Protocol-Defined Expedited Adverse Event Reporting Period

The protocol-specified reporting level continues throughout the study/trial period (from enrollment of a subject through the end of study follow-up visits for that subject). The protocol may also require the same level of adverse event reporting to be continued beyond the end of study follow-up for each subject, and if so, the protocol must specify the duration of this additional reporting period.

4.0 METHOD AND TIMEFRAME FOR EXPEDITED REPORTING OF INDIVIDUAL ADVERSE EVENTS

All information requested on the DAIDS Expedited Adverse Event Reporting Form must be provided and the form submitted to the DAIDS Safety Office. This form can be found at the web site for the DAIDS Safety Office. Contact information for the DAIDS Safety Office is provided in Appendix B. The timeframe for expedited reporting of individual adverse events begins when the

site recognizes that an event fulfills the criteria outlined in this Manual for expedited reporting to DAIDS. Sites must submit adverse events requiring expedited reporting to the DAIDS Safety Office as soon as possible, **but no later than 3 business days**, after the site's recognition that the event fulfills the criteria for expedited reporting.

5.0 ADDITIONAL EXPEDITED REPORTING REQUIREMENTS

5.1 Follow-up Reporting of Adverse Events

5.1.1 Submitting Follow-Up Information on Adverse Events

For the circumstances listed below, the site is required to submit follow-up information when it becomes available on a new Expedited Adverse Event Form as a Follow-up Report.

- Requests by DAIDS for additional information.
- A change in the relationship between the adverse event and study agent by the study physician.
- Additional significant information that becomes available for a previously reported adverse event. This is particularly important for new information addressing cause of death if the initial assignment was "pending."
- Results of rechallenge with the study agent(s), if performed.

5.1.2 Outcome of Adverse Events

The site **must** follow each reported adverse event and record eventual outcomes in the source documentation. However, report of the outcome of a reported adverse event to the DAIDS Safety Office is not required unless specifically requested by DAIDS.

5.2 Reporting Recurrent Adverse Events

For events that have been previously reported to the DAIDS Safety Office, if the event has fully resolved and then re-occurs to a level requiring expedited reporting, the adverse event must be reported as a New Report to the DAIDS Safety Office.

5.3 Reporting Change in Severity of Adverse Events

Any ongoing event that increases in severity to a higher grade than previously reported must be reported again as a New Report on a new DAIDS Expedited Adverse Event Reporting Form. Ongoing events that improve, but are not resolved and then increase in severity to the same or lower severity grade than previously reported do not have to be reported again to the DAIDS Safety Office. Resolution is the normalization or return to baseline (i.e., prior to study agent exposure) of laboratory values, signs, or symptoms related to the event.

5.4 Study Physician Assessment and Signature

A study physician listed on the Form FDA 1572 for IND studies or the DAIDS Investigator of Record Agreement (IoR) for non-IND studies must review and

verify the data on the DAIDS Expedited Adverse Event Reporting Form for accuracy and completeness. This physician also makes the site's final assessment of the relationship between the study agent and the adverse event. This physician must sign the completed DAIDS Expedited Adverse Event Reporting Form. If necessary to meet timely reporting requirements, sites can submit an expedited adverse event report without a completed signature page. However, the completed signature page, and necessary corrections or additions, must be submitted within the next 3 business days.

6.0 APPENDICES

6.1 Appendix A: Definition of Terms

Adverse Event (AE): An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH E6) (Synonym: Adverse Experience)

DAIDS Safety Office: The Office to which adverse events requiring expedited reporting are submitted. (DAIDS)

Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences (Toxicity Tables): Lists of common terms and severity (intensity) parameters used to describe adverse events occurring in DAIDS-sponsored clinical studies/trials. (DAIDS)

IND: An investigational new drug application. (21 CFR 312.3)

Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects. (ICH E6)

Non-IND Study/Trial: A study/trial for which there is no IND filed with the US FDA.

Package Insert: The approved package circular in marketed drug packaging containing the drug description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, dosage and administration, how drug is supplied, "clinical studies," and "references." (21 CFR 201.57)

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or

prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. (ICH E6 and E2A)

Study Agent: Drugs, biological products, or combination of drugs and biological products (approved or investigational) defined in the protocol as requiring expedited reporting to DAIDS. (DAIDS)

Study Physician: A physician listed on the Form FDA 1572 for IND studies or on the DAIDS Investigator of Record Agreement (IOR) for non-IND studies. (DAIDS)

Suspected Adverse Drug Reaction (SADR): An adverse event that could potentially have a causal relationship to a study agent (definitely, probably, possibly, probably not related or for deaths, pending). (DAIDS)

Toxicity: An adverse event that has an attribution of possibly, probably, or definitely related to a study agent. (DAIDS) NOTE: This term should not be used for expedited reporting of adverse events to DAIDS.

Unexpected Event: An adverse event, the nature or severity (intensity) of which is not consistent with the applicable product information (Investigator's Brochure, package insert, or summary of product characteristics for a US FDA-approved study agent. (DAIDS)

6.2 Appendix B: Contact Information for DAIDS Safety Office

All completed DAIDS Expedited Adverse Event Forms are submitted to the DAIDS Safety Office. For questions or other communication, please note the following:

Website: <http://rcc.tech-res-intl.com>
Office Phone*: 1-800-537-9979 (US only) or +1-301-897-1709
Office Fax*: 1-800-275-7619 (US only) or +1-301-897-1710
Office Email: RCCSafetyOffice@tech-res.com
Office Hours: Monday through Friday, 8:30 AM to 5:00 PM (US Eastern Time)
Mailing Address: DAIDS Safety Office
6500 Rock Spring Drive
Suite 650
Bethesda, MD 20817

*Office phone and fax are accessible 24 hours per day.

6.3 Appendix C: Summary Chart for Expedited Reporting of Adverse Events to DAIDS for Protocol-Specified Study Agents

	Standard Level	Intensive Level	Targeted Level
Deaths	All Events	All Events	All Events
Congenital anomalies, birth defects, fetal losses	All Events	All Events	All Events
Disabilities/Incapacities	All Events	All Events	All Events
Hospitalization¹	All Suspected Adverse Drug Reactions ²	All Suspected Adverse Drug Reactions ²	Unexpected Suspected Adverse Drug Reactions ^{2,3}
Other events	All Grade 4 Suspected Adverse Drug Reactions ²	All Grades 3 and 4 Suspected Adverse Drug Reactions ²	Unexpected Life-Threatening Clinical Suspected Adverse Drug Reactions ^{2,3}

¹This category includes hospitalization, prolongation of hospitalization or requirement of intervention to prevent permanent disabilities or death.

²Suspected adverse drug reactions are adverse events that are assessed as definitely, probably, possibly, probably not related to a study agent (or for deaths, pending).

³Unexpected events are adverse events, of a nature or severity (intensity) that is not consistent with the applicable product information (package insert/summary of product characteristics) for a US FDA-approved study agent.

Timeframe for Expedited Reporting of Individual Adverse Events:

Adverse events requiring expedited reporting are to be reported to the DAIDS Safety Office **no later than 3 business days** after the site's recognition that the event fulfills the criteria for expedited reporting.

Protocol-Defined Expedited Adverse Event Reporting Period

The protocol-specified reporting level continues throughout the study/trial period (from enrollment of a subject through the end of study follow-up visits for that subject). The protocol may also require the same level of adverse event reporting to be continued beyond the end of study follow-up for each subject.

APPENDIX V: SAMPLE INFORMED CONSENT DOCUMENT (SCREENING)

Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

Version 3.0
30 June 2008

PRINCIPAL INVESTIGATOR: [insert]
PHONE: [insert]
Short Title for the Study: Safety and Acceptability of VivaGel® in Sexually Active Women

Introduction

You are being asked to take part in these screening exams and tests because you are a sexually active woman between the ages of 18 and 24 years, and you may be able to join the research study named above. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. The screening exams and tests include interview questions, urine and blood tests, a physical exam, and an examination of your vagina.

This is a consent form. It gives you information about the screening exams and tests. The study staff will explain the exams and tests to you and what is expected of you. You are free to ask questions about the screening exams and tests at any time. If you agree to have the screening exams and tests, you will be asked to sign this consent form in front of a witness. You will be given a copy of this form to keep.

Why Are These Screening Exams and Tests Being Done?

The main purpose of these screening exams and tests is to find out if you can join a research study. The research study will try to find out if VivaGel® is safe and if there are any bad effects when women apply VivaGel® in the vagina for 2 weeks. About one-third of the women in the research study will place VivaGel® into the vagina twice a day for two weeks. One-third of the women will place a VivaGel® placebo (inactive) gel into the vagina twice a day for two weeks, and one-third will place a different kind of placebo (inactive) gel, called HEC placebo, into the vagina twice a day for two weeks. Women will be in the group getting VivaGel®, the group getting VivaGel® placebo gel or the group getting HEC placebo gel, depending on a selection process that will use random chance (like flipping a coin) to decide the groups. The other purposes of the study are to see if an ingredient in the gel (SPL7013) goes into the bloodstream, to find out what women think about the study gel, and to see if women use the gel according to the study directions.

VivaGel[®] study gel is “experimental”. This means we do not know all the effects it may have. We do not know if it will be safe and tolerated in all women. This is one of the reasons the study is being done. Because the study gel is experimental, the United States Food and Drug Administration (FDA) and [LOCAL AUTHORITY] [HAS/HAVE] not approved it for use in the general community. The FDA has been informed of this study and has allowed it to happen. The [local authority] has also allowed the study to happen.

Before a large study can be done to find out if VivaGel[®] stops HIV from getting into the body, we must first make sure it is safe. So far, the safety of the study gel has been tested among 37 women in Australia. 36 of these women applied the gel in the vagina every day for one week, and one woman did not finish the study because of an abnormal test result from the time before she started the gel. In that study, the gel was shown to be safe and women in the study did not have a lot of complaints or problems. The most common complaints were mild abdominal pain. Some women also noticed that the gel leaked out of the vagina. None of these women had any SPL7013 from the VivaGel[®] in their bloodstream according to the tests that were done.

The United States National Institutes of Health is providing funds for this study to take place. A total of approximately 61 women from Florida and Puerto Rico will join this study (about 30 in Florida and about 30 in Puerto Rico). About 30 women will be in the study here at [INSERT NAME OF SITE]. The whole study will take about ten months to finish. Each woman will be in the study for about eight weeks. It will take about one week to one month to complete the screening exams and tests. Some people may not be able to join the study because of information found during the screening exams and tests. If you can join the study, it will take about three weeks to complete the main study exams and tests. Once enrolled in the study, you will be asked to use the study gel twice a day, everyday, for two weeks. You will have a study visit every week for two weeks, and then a study visit about one week after you finish using the study gel.

What Do I Have To Do If I Take Part in the Screening Exams and Tests?

If you agree to have the screening exams and tests, you will have one or two screening visits here at the study site. The exams and tests will take about one week to one month. Depending on what your screening exams and tests show, more screening visits may be needed. All screening exams and tests will be done within 36 days. If all exams and tests are not done within 36 days, and you still want to find out if you can join the research study, you will have to start the screening exams and tests over from the beginning.

- **Answering Questions**

Your first visit will continue today, after you read, discuss, and sign this form. No study exams or tests will be started before the screening exams and tests have been fully explained to you and you have signed this form. The visit will take about one to two hours. To find out if you can join the

study you will be asked some questions. The questions will be about you and where you live. You will be asked questions about your health, the medicines you take, your periods, and your sexual practices. Some people may be embarrassed by questions about their sexual practices.

- **Pregnancy Test**
If your answers to the questions show that you may join the study, you will have to give urine for a pregnancy test. You will receive the result of your pregnancy test today. If you are pregnant, you will not be able to join the study. However, site staff will talk to you about options available to you. They will refer you to available sources of medical care and other services you may need. If the study is still open after your pregnancy, you can come back here to find out if you can join the study then.
- **Tests for HIV and Sexually Transmitted Infections**
If you are not pregnant, study staff will talk to you about HIV and other sexually transmitted infections or sexually transmitted diseases (commonly known as STIs or STDs). You will have a blood test for HIV, and syphilis, vaginal swabs for bacterial vaginosis, candidiasis, and trichomoniasis and a urine test for gonorrhea and Chlamydia. You will talk about HIV/AIDS and other STIs. You will also talk about ways that HIV and other STIs are spread, and ways to protect against them. You will talk about what it may mean to know the results of these tests. You can discuss whether you are prepared to receive the test results. If you are having health problems that may be due to STIs, the study staff will refer you for treatment.
- **Using an Effective Birth Control Method Plus Condoms**
The study gel is not a birth control method. You must agree to use an effective method of birth control such as birth control pills, birth control shots (such as Depo-Provera) or the birth control patch, an intrauterine device (or IUD), be sterilized, or have sex with a partner who is sterilized. You must also be willing to continue to use birth control for one month after you stop applying the study gel. An intrauterine device (IUD) is a small object that is inserted through the cervix and placed in the uterus to prevent pregnancy. If you are using an IUD for birth control and want to join the study, you must have had it put in at least 30 days ago in order to join the study. The study staff will provide male condoms to you free of charge. However, condoms are not considered an adequate means of birth control for the purposes of this study.
- **Blood and Urine Tests**
If you are willing to have HIV and STI testing, you will give blood (about 30 mL or two tablespoonfuls) [LOCAL EQUIVALENT - SITES TO COMPLETE] and urine for the tests. Your blood will be tested for HIV. You must know what your HIV test result is to join the study. Your blood will also be tested to

check on your general health, including the health of your liver, kidneys and blood. Your urine will also be tested for infections. It takes about [X AMOUNT OF TIME - SITES TO COMPLETE] before your results are ready. We will give you your results as soon as they are available.

- **Physical and Pelvic Exams**

You will have a physical exam and a pelvic exam. During the pelvic exam the study doctor or nurse will use a speculum as is usual in collecting a Pap smear. They will check for discharge, or other signs of infection, and other possible problems. The study doctor or nurse will also take some vaginal swabs to test for STIs and other possible problems.

If a sore (or other problem) is seen during the examination of your vagina, you may need medicine to treat it. You will be asked to see your regular health care provider for medicine or may be given medicine here. We will ask you to come back here after a few days for another exam. If the sore (or other problem) has cleared up when you come back, you may be able to join the research study.

- **Pap Test**

The study staff will also collect samples from your cervix for a “Pap test” or “Pap smear”. If the test is abnormal, it could mean you have cervical cancer, or that you should have more tests or treatment to lower your chances of having it turn into cervical cancer. It takes about [X AMOUNT OF TIME – SITES TO INSERT] before Pap test results are ready. If you have a written report confirming a normal Pap smear in the last year you will not need to have a Pap smear taken at this screening visit. The results of your Pap test may affect whether or not you can continue in the study.

- **Test Results**

It takes about [X AMOUNT OF TIME – SITES TO INSERT] before HIV, STI, and Pap test results are ready. We will give you the results for all your exams and tests at your next appointment. You will talk with the study staff about the meaning of your test results and how you feel about them.

If your tests show that you have HIV you will not be able to join the study. The study staff will refer you to available sources of medical care and other services you may need for HIV. They will tell you about other studies that you may be able to join. If your exams and tests show that you have an STI, you will need medicine to treat it. The study staff will refer you to your usual health care provider for medicine or may give you medicine here to treat the STI. You will not be able to join the research study if your tests show you have an STI. However, if you have had outbreaks of genital herpes in the past, but do not have any on your exam today, you may be able to join the research study.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE:]

[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed during sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [HEALTH AUTHORITY].

If your exams and tests show no problems, you will be able to enter the research study. You will receive a different Informed Consent Form if you return for the Enrollment Visit. If at any time during the screening it is found that you cannot join the study, the screening process and your visit will end.

Why Would The Doctor Stop the Screening Procedures Early?

The study doctor may need to stop the screening exams and tests early without your permission if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), U.S. National Institutes of Health (NIH), the drug company supporting this study, the Ethics Committees, the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants).
- Your exams, tests and answers to the questions show you cannot join the study.
- The study staff feels that having the screening exams and tests would be harmful to you.
- You do not want to find out your HIV test result.
- You are not able to come to the visits or complete the screening exams and tests.
- Other reasons that may prevent you from completing the study.

What Are The Risks Of The Screening Visit Tests?

Risk of Blood Draws:

You may feel discomfort or pain when your blood is drawn. You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

Risk of Genital Exams:

You may feel discomfort or pressure during the exam of your genital area and inside your vagina. You may have mild vaginal spotting (bleeding). The mild bleeding will stop shortly after the exam.

Other Possible Risks:

You may become embarrassed, worried, or nervous when discussing how you have sex; ways to protect against HIV and other infections passed during sex, and your test results. You may become worried or nervous while waiting for your

test results. If you have HIV or other infections, knowing this could make you worried or nervous. A trained counselor will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy while you are having the screening exams and tests. Your visits here will take place in private. However, it is possible that others may learn that you are taking part in the study here. Because of this, they may treat you unfairly. For example, you could have problems getting or keeping a job, or being accepted by your family or community.

Are There Benefits To Taking Part In This Study?

You may get no direct benefit from the screening exams and tests. However, you will have a physical exam and a pelvic exam, and counseling and testing for HIV and STIs. You will also have tests to check your general health and the health of your liver, kidneys, and blood. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If your Pap test result is not normal, you will be referred for treatment at the [INSERT NAME OF PROVIDER/CENTER].

You will get counseling and testing for HIV. You will get free male condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your own health care provider or we will provide you with a referral to a center where you can receive appropriate care. You will get counseling and testing for STIs and other infections. If you have any of these infections, you will be referred for treatment if needed. You can bring your male partner(s) here so that we can also provide them with referral for diagnosis and treatment for potential STIs.

What Other Choices Do I Have Besides This Study?

You do not have to participate in this study, if you choose not to do so.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community for which you may be eligible. If you wish, we will inform you about other studies that are being conducted locally. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] Please talk to your doctor about these and other choices that may be available to you.

What About Confidentiality?

Efforts will be made to keep your personal information private. We cannot guarantee absolute confidentiality. If this study is published, your name will not be used and you will not be personally identified.

Your records may be reviewed by:

- The U.S. Food and Drug Administration (FDA)
- U.S. National Institutes of Health (NIH)
- [INSERT NAME OF SITE] IRB
- Study staff
- Study monitors
- Ethics committees
- Drug companies supporting this study

In addition to the efforts of the study staff to help keep your personal information private, a Certificate of Confidentiality has been obtained from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your taking part in the study. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities. You are encouraged but not required to tell sexual partners about your being in this study.

What Are The Costs To Me?

There is no cost to you for the screening exams and tests.

Will I Receive Any Payment?

You will be paid for your time and effort for each screening visit. You will receive [INSERT SITE - SPECIFIC AMOUNT OF MONEY] for each visit. You will also be paid for other costs to you for coming to the screening visits [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE]. There may be one or more screening visits.

What Happens If I Am Injured?

It is unlikely that you will be injured as a result of having the screening exams and tests. If you are injured as a result of having the screening exams and tests, you will be given immediate treatment for your injuries. However, you may have to pay for this care. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.
[SITES TO SPECIFY INSTITUTIONAL POLICY]

What Are My Rights As A Research Participant?

Taking part in the screening exams and tests is completely voluntary. You may choose to not have the screening exams and tests any time. You will be treated the same no matter what you decide. If you choose to not have the screening exams and tests, you will not lose the benefit of services to which you would normally have at this clinic.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

What Do I Do If I have Problems or Questions?

For questions about the screening exams and tests or if you have a research-related injury, you should contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURE PAGE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

**APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT
(ENROLLMENT)**

**Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel
(VivaGel®) Applied Vaginally in Sexually Active Young Women**

**Version 3.0
30 June 2008**

PRINCIPAL INVESTIGATOR: [insert]
PHONE: [insert]
Short Title for the Study: Safety and Acceptability of VivaGel® in Sexually Active Women

Introduction

You are being asked to take part in this research study because you are a sexually active woman between the ages of 18 and 24 years and have passed the screening tests for this study. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to join this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this form to keep.

Why Is This Study Being Done?

You may have heard of this study before since this study began enrolling participants in August 2007, but was paused for a short time because some participants had some side-effects that were probably caused by the gel. The researchers decided to stop the study for a little while so that they could study these side-effects to make sure the gel was safe to use. The researchers found that the side-effects were minor and the participants got better quickly. These types of side-effects are normal for this kind of study. At the beginning of this study, the researchers were comparing 2 different products-VivaGel® and VivaGel® placebo, a gel with the same ingredients as VivaGel®, but without the active study drug. The new version of this study includes a second kind of placebo gel called HEC gel. Several other studies have shown HEC gel to be safe and well-tolerated in humans. Because of this, it is used as the comparison product in many other microbicide studies. The addition of HEC gel to this study will help the researchers understand the effects of VivaGel® and the VivaGel® placebo.

This research study will try to find out if VivaGel[®] is safe and if there are any bad effects when women apply VivaGel[®] in the vagina for 2 weeks. About one-third of the women in the research study will place VivaGel[®] into the vagina twice a day for two weeks. One-third of the women will place a VivaGel[®] placebo (inactive) Gel into the vagina twice a day for two weeks, and one-third will place a different kind of placebo gel called HEC placebo gel into the vagina twice a day for two weeks. Women will be in the group getting VivaGel[®], the group getting VivaGel[®] placebo gel, or the group getting HEC placebo gel, depending on a selection process that will use random chance (like flipping a coin) to decide the groups. The other purposes of the study are to see if an ingredient in the gel (SPL7013) goes into the bloodstream, to find out what women think about the study gel, and to see if women use the gel according to the study directions.

VivaGel[®] is “experimental”. This means we do not know all the effects it may have. We do not know if it will be safe and tolerated in all women. This is one of the reasons the study is being done. Because the study gel is experimental, the United States Food and Drug Administration (FDA) and [LOCAL AUTHORITY] [HAS/HAVE] not approved it for use in the general community. The FDA has been informed of this study and has allowed it to happen. The [local authority] has also allowed the study to happen.

Before a large study can be done to find out if VivaGel[®] stops HIV from getting into the body, we must first make sure it is safe. So far, the safety of the study gel has been tested among 37 women in Australia. 36 of these women applied the gel in the vagina every day for one week, and one woman did not finish the study because of an abnormal test result from the time before she started the gel. In that study, the gel was shown to be safe and women in the study did not have a lot of complaints or problems. The most common complaints were mild abdominal pain. Some women also noticed that the gel leaked out of the vagina. None of these women had any SPL7013 from the VivaGel[®] in their bloodstream according to the tests that were done.

The United States National Institutes of Health is providing funds for this study to take place. A total of 61 women from Florida and Puerto Rico will join this study (about 30 in Florida and about 30 in Puerto Rico). About 30 women will be in the study here at [INSERT NAME OF SITE]. The whole study will take about ten months to finish. Each woman will be in the study for about eight weeks. It will take about three weeks to complete the main study exams and tests. If you can join the study, you will be asked to use the study gel for two weeks. You will have a study visit every week for three weeks, though you or the study staff may request additional visits if they are needed.

What Do I Have To Do If I Am In This Study?

If you decide to join this study, and your tests and answers to the questions show you can join, you will be placed in one of three study groups. One group will get VivaGel[®], one group will get VivaGel[®] placebo, and one group will get HEC

placebo gel. All three groups will use the study gel twice daily for 14 days. The study group will be chosen by chance, like flipping a coin, or throwing dice [SITE TO MODIFY TO LOCAL EQUIVALENT]. You cannot choose your group, and the study staff cannot choose your group for you. You have an equal chance of being placed in either of the groups. Neither you nor the study staff will know whether you are in the placebo or VivaGel® groups.

All three groups are important to this study. No matter which study group you are in, you must remember that we do not know if any of the study gels work to protect women from getting HIV. The only known way to protect against getting HIV during sex is to use a male condom every time you have sex.

It is not known if the study gel will work to protect against pregnancy, therefore you should not use the study gel as a birth control method. You must agree to use an effective method of birth control such as birth control pills or another hormonal based method (except for vaginal rings), an intrauterine device (or IUD), be sterilized, or have sex with a partner who is sterilized as well as using condoms.

The pharmacy will provide male condoms and panty liners to you free of charge. Each visit is described below. You should continue to use the gel if you get your period. If you have your period at the time of your visit, you will complete all visit exams and tests except for the pelvic exam and associated tests (which may be made up once your period is over). You will insert into the vagina one full applicator, about 3 and a half grams (or about one teaspoonful), of the study gel. You will use the study gel twice a day for 2 weeks, as long as the study staff thinks it is safe for you to keep using the gel after your first week.

Once you join the study, you will return to the site for a follow up visit after one week, two weeks, and three weeks. After two weeks you will stop using the study gel. You will return all of your unused applicators to the study sites at the Week 1 and Week 2 visits in the bags given to you for this purpose. In total, you will have at least four study visits including today's visit.

After all the participants finish the study, and we find out the results of the study, if you wish, you will be told which study gel you received. We will also provide you with a brief summary of the main findings from the study.

Enrollment Visit:

If you decide to take part in this study, your first visit will continue today, after you read, discuss, and sign this form. No study procedures will be started before the visit exams and tests have been fully explained to you and you have signed this form. Today's visit will take about one to one and a half hours.

To find out if you still can join the study you will be asked some questions – the questions will be about you, where you live, and other questions about your health, your periods, alcohol and substance use, the medicine you take, and your sexual practices. Some people may be embarrassed by questions about their sexual history.

If your answers to the questions show that you can join the study, you will:

- Give urine for a pregnancy test if your second screening visit took place on a day other than today. You will be given your result for the pregnancy test today. If you are pregnant, you will not be able to join the study; however site staff will talk to you about options available to you, and will refer you to available sources of medical care and other services you may need. If the study is still open after your pregnancy, you can come back here to find out if you can join the study then.
- Give blood for tests to check on the health of your blood cells, liver, and kidneys and to confirm that there is no SPL7013 already in your blood (about 30 mL or about 2 tablespoons).
- Have a pelvic exam. The study doctor or nurse will use a speculum. The doctor or nurse will check the vagina and cervix for discharge, or other signs of infection, and other possible problems. During the pelvic exam, the study doctor or nurse will look at your genital area and into your vagina through a lens called a colposcope. The lens works like a magnifying glass to help the nurse or doctor see anything that may not be normal. The lens will not be inside your body. They may take digital video pictures of the colposcopy with a camera. You may tell the study staff not to record these images. These images will be kept strictly confidential and used only by study physicians to decide upon the significance of possible changes in the vagina or cervix. The study doctor or nurse may also take some fluids to test for sexually transmitted infections or sexually transmitted diseases (commonly known as STIs or STDs) and other possible problems if they feel this is necessary.
- Have an abdominal exam and vital signs (blood pressure, pulse, and temperature).
- The study doctor or nurse will collect swabs from the vagina and cervix to measure the level of immune activity in the vagina and to check that there is a healthy balance of bacteria in the vagina.

If a sore (or other problem) is seen during the examination of your vagina, you may need medicine to treat it. You will be asked to see your regular health care provider for medicine or be given medicine here. We may ask you to come back

here after a few days for another exam. If the sore (or other problem) has cleared up when you come back, you may be able to join the research study.

It takes about [X AMOUNT OF TIME – SITES TO INSERT] before these tests are ready. We will give you the results from all the exams and tests after they are ready. You will talk with the study staff about the meaning of your test results and how you feel about them.

If your exams and tests show that you have an STI, you will not be eligible to join the study. The study staff will refer you for treatment of the infections. You will be asked to come back here for a check-up after taking all the medicine.

If you are eligible to join the study, you will be given 20 tubes of either VivaGel® or placebo gel (VivaGel® placebo or HEC placebo) already packaged inside applicators. You will also be given instructions on how to use them. You will receive male condoms, and panty liners and/or menstrual pads. You will insert your first dose of gel while you are in the study clinic.

In addition to your study visits, you will be asked **to do** the following:

- Use an effective method of contraception during the study.
- Contact the study doctor or nurse if you have any discomfort or medical problems.
- Tell the study staff about any medications you take while in the study.
- Agree to use study provided panty liners and/or menstrual pads for your period or in case the study gel leaks out of the vagina. If you need a different kind other than the kind provided to you by the study, let the study staff members know.
- You **must not** use spermicides or male condoms lubricated with spermicides during the study. If you need to use a different kind other than the ones provided to you by the study, let the study staff know.
- It is ok for you to use tampons, take a bath or go swimming while you are using the study gel.

You **must not** do the following during the entire time while in the study:

- Breastfeed
- Use intravenous drugs except for medical use.
- Take part in studies of other vaginal products or any drug or device study. Tell the study staff if you plan to join another study.
- Use other participants' study gel.
- Douche or otherwise clean the vagina, or insert other products into your vagina.
- Practice the following types of sexual activity during the two weeks you are receiving the gel:
 - Oral – vaginal sex (known as cunnilingus)

- Penile – anal intercourse
- Penile – vaginal intercourse **without** your partner using an approved condom

Telephone Call

Two days after you have your Enrollment Visit, you will have a phone call with the study staff to talk about any problems you might have with the gel applicator. You can call the clinic, or the study staff can call you, depending on how you want to arrange it. This call will probably take about 5 minutes or less.

One-Week Clinic Visit:

This visit will take about an hour. The visits will not be scheduled during your period. You will have the following procedures at your One-Week Clinic Visit:

- Tell the study staff any updated information about your address, telephone number or other contact information.
- Tell the study staff if you had any medical problems or discomfort since your last visit.
- Tell the study staff any new information about your health or your periods.
- Tell the study staff about any medicines you are taking.
- Give urine for a pregnancy test. You will receive the results of your pregnancy test on the day of the visit.
- Complete a computerized questionnaire about your use of the study gel.
- Tell the study staff your thoughts and opinions about the study gel.
- Have an abdominal exam and vital signs (blood pressure, pulse, and temperature).
- Have a pelvic exam with a speculum with collection of swabs from the vagina and cervix.
- Give blood (about 25 mL or a little more than 1 and a half tablespoonfuls) [OR LOCAL EQUIVALENT – SITE TO INSERT]. We will check your blood for the overall health of your blood cells, and the health of your liver and kidneys, the study staff will give you the results of your tests [IN X AMOUNT OF TIME – SITES TO INSERT].
- Receive 10 more tubes of gel (we expect that you may have extra tubes left over at the end of the study that we want you to return to the clinic)

Two-Week Clinic Visit:

This visit will take about an hour and a half. You will stop applying the study gel at this visit. You will complete all of the 1-Week Follow-Up procedures plus:

- Have a pelvic exam with a speculum, and with a colposcopic lens;
- Have a blood test to see if SPL7013 can be measured in your blood;
- Complete a computerized questionnaire about your experiences using the study gel including its use during sex;
- Return all of your unused (if you have any unused) applicators to the clinic.

Three-Week Clinic or Termination Visit:

This visit will take about an hour. At this visit you will:

- Have an abdominal exam and vital signs (blood pressure, pulse, and temperature);
- Have a pelvic exam with a speculum, and have some vaginal and cervical swabs taken;
- Complete a computerized questionnaire about your thoughts and opinions about the study and how easy or difficult it was to be in the study.

The study site staff will give you your test results as soon as they are available. We will ask you to come back to the clinic or, with your permission; we may visit you at your home or a place in your community.

After You Finish Using the Study Gel:

During this study you may have a chance to take part in additional studies. If you choose not to take part in any of our additional studies, your participation in this study remains the same. If you have any problems or concerns regarding your health after using the study gel, let the study staff members know. You can contact the study site staff at any time after you have finished using the study gel. The study site staff will want to let the study sponsor know about any serious problems you tell them about.

Any Time During The Study:

If either you or the study staff members think you may have become pregnant, you will give urine for a pregnancy test. Also, if you are having health problems that may be caused by STIs, you will:

- Have an exam of your genital area and inside your vagina.
- Give blood or urine to test for STIs.
- Get referral for treatment for STIs if you need it.

You are asked to tell the study staff about any medical problems you have, especially genital problems. You can contact the study staff between regular visits to report these problems. The study staff will examine you as necessary. They will refer you for medical care that you may need.

You are also encouraged to tell the study staff if your partner has any genital problems after you have had intercourse during the study. If this kind of problem occurs, your partner or partners may contact the study site staff for a check-up.

If the staff members find that a study gel is causing you problems, they may ask you to stop using the study gel, either for a short time or permanently. The study staff will ask you to stop using the study gel if you become pregnant or if you become infected with HIV. Even if you stop using the study gel, you will be asked

to stay in the study and have your follow up visits. You will also have some or all of the originally planned exams and tests that the study staff would like you to have to check on your health.

If you have an STI that your partner also may have, you can bring him here for counseling and referral for testing and treatment. You can have extra counseling and testing for HIV at any time during the study. If you wish, your partner can have counseling with you. If you become infected with HIV, you can stay in the study but you cannot keep using the study gel and you should return any used and unused applicators to the study clinic. The study staff will give you counseling and refer you to available sources of medical care and other services you may need.

At each study visit, the study staff will update information on where you live and how to keep in contact with you. They will use this information to remind you of scheduled visits. If you miss a visit, the study staff will try to contact you by [SITE-SPECIFIC METHODS]. If you give your permission, they also may visit your home to find you. They will try to reach you through the contact people that you list. If they talk to these people, they will not tell them why they are trying to reach you.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE:]

[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed during sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [HEALTH AUTHORITY].

How Many Women Will Take Part In This Study?

61 women will take part in this study. About 30 women will be from Florida and about 30 women will be from Puerto Rico.

How Long Will I be In This Study?

You will be in this study about six weeks. You will be asked to apply the study gel for 2 weeks. The total time you will be in the study, including the time to complete the screening exams and tests and the main study is about six weeks.

Why Would The Doctor Take Me Off This Study Early?

The study doctor may need to take you off the study early without your permission if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), U.S. National Institutes of Health (NIH), the drug company supporting this study, the Ethics Committee, the local government or regulatory agency,

- or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants).
- The Data and Safety Monitoring Board (DSMB) or Study Monitoring Committee (SMC) recommends that the study be stopped early (A DSMB is an outside group of experts who monitor the study; a SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study).
 - You are not able to keep appointments or apply study gel as instructed.
 - Other reasons that may prevent you from completing the study successfully.

The study doctor will ask you to stop using the study gel but continue to come in for your follow up visits and procedures if:

- You are pregnant.
- You are breastfeeding.
- You become infected with HIV.
- The study doctor decides that using the study gel would be harmful to you or your partner.
- You require a treatment that you may not take while using the study gel.
- You have a bad reaction to the study gel.

If the study doctor asks you to stop using the study gel, you will still be advised to come in for all of the scheduled follow-up visits that are described above, including things like the abdominal exam, vital signs, pelvic exam, colposcopy, blood tests, and questionnaires. You will stop using the study gel until the study doctor decides it is safe for you to start using the study gel again, if possible.

What are the risks of this study?

Risks of Blood Draws:

You may feel discomfort or pain when your blood is drawn. You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

Risk of Genital Exams:

You may feel discomfort or pressure during the exam of your genital area and inside your vagina. You may have mild vaginal spotting (bleeding). The mild bleeding will stop shortly after the exam.

Other Possible Risks:

You may become embarrassed, worried, or nervous when discussing sexual behaviors and HIV. You may become worried or nervous while waiting for your STI and HIV test results. If you have HIV, knowing your HIV status could make you worried or nervous. You will talk with a trained staff member who will help you deal with any feelings or questions you have.

Risks of VivaGel®

It is very important to use the study gel as instructed by staff. The study gel used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship to the study gel. If you have questions concerning additional study drug side effects please ask the study staff at your site.

Some of the effects of VivaGel® are still unknown. Some possible effects are dryness, itching, burning, redness, a sore or pain in the genital area. You may also have discharge if the study gel comes out of the vagina. The study staff will give you panty liners and/or menstrual pads in case you need them.

Your male sexual partners will be protected from potential risks associated with exposure to VivaGel® through:

- Consistent use of approved condoms during penile-vaginal sex
- Avoidance of oral-vaginal sex

Possible Risks to Your Privacy

We will make every effort to protect your privacy while you are in this study. However, it is possible that you could have problems if people learn that you are in this study. They might think that you are infected with HIV or at risk of HIV because of sexual behavior or illegal drug use. Because of this, others may treat you unfairly. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community. There also is a risk to your privacy if someone else taking part in this study knows you.

Are There Risks Related To Pregnancy?

Because there is no information on VivaGel® in pregnant women, VivaGel® should not be used during pregnancy. You must agree to try to not become pregnant during the study. It is not known if the study gel used in this study harms unborn babies. You and your partner must be willing to use an effective method of birth control such as birth control pills or another hormonal based method (except for vaginal rings), an intrauterine device or IUD, be sterilized, or have sex with a partner who is sterilized. You should discuss this with the study staff. You must be willing to continue to use birth control for one month after you stop applying the study gel.

The study staff will provide male condoms to you free of charge. If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant.

What If I Have A Positive Pregnancy Test During The Study?

If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices. If you have a

positive pregnancy test while using the study gel, we will ask you to stop using the study gel and return all used and unused applicators, but will ask you to continue to be in the study and to come in for your follow up visits. There are no anticipated additional risks to you if you choose to continue to take part in this study.

If you are pregnant and choose to continue the pregnancy, this study will not provide care related to your pregnancy, the delivery of your baby, or the care of the baby. Your baby may have been exposed to SPL7013 if you received VivaGel[®], and if it was absorbed from the vagina into your blood, and we do not know if this will affect unborn babies. The study staff will contact you to ask you a few questions about the outcome of your pregnancy. You must arrange for your care and your baby's care outside of this study. This study cannot provide care related to termination of pregnancy, though study staff can provide you with information regarding your access to termination of pregnancy as part of counseling you about your pregnancy test results.

Breastfeeding

It is unknown if there are any effects of VivaGel[®] on breast milk. It is unlikely that the study gel will pass through breast milk but absorbing the study gel from the vagina into the blood may affect breast milk and may cause harm to your infant. You must agree to not breastfeed during this study. Women who are currently breastfeeding are advised to not enroll in this study.

Are There Benefits To Taking Part In This Study?

There is no direct benefit to you because no one knows if the study gel will prevent HIV infection. Also, you may be in the study group that receives the placebo gel, which will not help in preventing HIV. Information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive pelvic exams and counseling and testing for HIV and STIs. You will also have tests to check the overall health of your liver, kidneys, and blood cells. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If your Pap test result shows anything that is not normal, you will be referred for advice and/or treatment.

You will get counseling and testing for HIV. You will get free male condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your own health care provider or we will provide you with referral to a Center that can provide you with appropriate care. You will get counseling and testing for STIs. If you have an STI diagnosed, you will get medicine to treat them, if needed. You can bring your partner here for counseling and referral for testing and treatment for STIs if this is needed.

What Other Choices Do I Have Besides This Study?

You do not have to participate in this study, if you choose not to.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] Please talk to your doctor about these and other choices that may be available to you.

What About Confidentiality?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- The U.S. Food and Drug Administration (FDA)
- U.S. National Institutes of Health (NIH)
- [INSERT NAME OF SITE] IRB
- Study staff
- Study monitors
- Ethics committees
- Drug companies supporting this study

In addition to the efforts of the study staff to help keep your personal information private, a Certificate of Confidentiality has been obtained from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your taking part in the study. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities. You are encouraged but not required to tell your sexual partners about your being in this study.

What Are The Costs To Me?

There is no cost to you for study related visits, study products, physical examinations, laboratory tests or other procedures.

Will I Receive Any Payment?

You will receive payment for your time and effort in this study. You will receive [INSERT SITE-SPECIFIC AMOUNT OF MONEY] per visit. You will also receive payment for activities affected by your participation in this study [SUCH AS CHILD CARE, TRAVEL, LOSS OF WORK TIME – SITES TO COMPLETE].

What Happens If I Am Injured?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. However, you or your insurance company may have to pay for this care. This institution or the U.S. National Institutes of Health (NIH) does not have a program to provide money for your injuries. You will not be giving up any of your legal rights by signing this consent form.
[SITES TO SPECIFY INSTITUTIONAL POLICY]

What Are My Rights As A Research Participant/Volunteer?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. You will be treated the same no matter what you decide. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic. We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

What Do I Do If I have Problems or Questions?

For questions about this study or a research-related injury, contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURE PAGE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

APPENDIX VII: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)

Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

**Version 3.0
30 June 2008**

PRINCIPAL INVESTIGATOR: [insert]
PHONE: [insert]
Short Title for the Study: Safety and Acceptability of VivaGel® in Sexually Active Women

INTRODUCTION

You have decided to take part in a Division of AIDS research study. While you are in this research study there may be some samples of blood and/or fluid from your cervix taken from you that might be useful for future research. You are being asked to agree to the storage of these samples. This consent form gives you information about the collection, storage and use of your samples. The study staff will talk with you about this information. Please ask any questions, if you have some. If you agree to the storage of your samples, you will be asked to sign this consent form. You will be given a copy of this form copy to keep.

HOW WILL YOU GET THE SAMPLES FROM ME?

The research doctors want to save any extra blood and cervical fluid leftover from your tests during the study. This leftover blood and cervical fluid will be kept and used for future research.

HOW WILL YOU USE MY SAMPLES?

Your samples will be used to look for evidence of your body's response to infection (such as examining cells, proteins, and other chemicals in your body) while you were using the study gel and after you stopped using the study gel. Tests may also include examining your genes (DNA), since they might affect your response to disease in important ways. Your genes might make you more or less likely to becoming infected, affect your responses to infection, or make your responses to treatment stronger or weaker. No other kinds of genetic test will be done by anyone on your stored specimens without first explaining the test to you and getting your permission. The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored samples. This is because research tests are often done with experimental procedures, so the results from one research study are generally not useful for making decisions on managing your health. Should a rare situation come up where the researchers decide that one of the test results would provide important information for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you wish to be contacted with this type of test result, you must

give the study doctor or nurse any change to your address and/or phone number. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name, address and phone number. Your samples will not be sold or used directly to produce products that can be sold for profit.

Research studies using your samples will be reviewed by the National Institutes of Health, and Ethics Committee, and a special committee at the researcher's institution (an Institutional Review Board) whose purpose is to protect you as a research participant.

HOW LONG WILL YOU KEEP MY SAMPLES?

There is no time limit on how long your samples will be stored.

HOW WILL MY SAMPLES BE STORED?

Your samples will be stored at special facilities that are designed to store samples safely and securely. The storage facilities are designed so that only approved researchers will have access to the samples. Some employees of the storage facilities will need to have some access to your samples in order to store them and to keep track of where they are, but these people will not have information that directly identifies you. An Institutional Review Board will oversee the storage facilities to protect you and other research volunteers from harm.

DOES STORAGE OF MY SAMPLES BENEFIT ME?

There are no direct benefits to you.

WHAT ARE THE RISKS?

There are few risks related to storing your samples. When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes) it could cause you problems with your family (having a family member learn about a disease that may be passed on in families or learning who is the biological parent of a child) or problems getting a job or insurance.

WHAT ABOUT CONFIDENTIALITY?

In order to keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records.

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate

means that researchers cannot be forced to tell people who are not connected with the research, such as the court system, about your participation. Also, any publication of the research will not use your name or identify you personally.

People who may review your records include: [INSERT NAME OF SITE] IRB, National Institutes of Health (NIH), study staff, study monitors, and their designees. Having a Certificate of Confidentiality does not prevent you from giving information about yourself and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

WHAT ARE MY RIGHTS?

Allowing your samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study. If you decide now that your samples can be stored for future research, you may change your mind at any time. You must contact your study doctor or nurse and let them know that you do not want your samples used for future research. Your samples will then not be used and will be destroyed.

WHAT DO I DO IF I HAVE QUESTIONS?

For questions about the storage of your samples, contact (*insert the name of the investigator*) at (*insert telephone number*).

For questions about your rights related to the storage of your samples for research, contact (*insert the name or title of person on the Institutional Review Board*) at (*insert telephone number*).

SIGNATURE PAGE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

REFERENCES

1. UNAIDS. 2007 AIDS Epidemic Update: Global Summary. http://www.unaids.org/en/HIV_data/2007EpiUpdate/default.asp accessed December 18, 2007.
2. Frechet JM, Tomalia DA. Dendrimers and Other Dendritic Polymers. Chichester: Wiley; 2001.
3. Starpharma PL. Investigator's Brochure: SPL7013 Gel (VivaGel™) Version CIB-001-05; 2006.
4. McCarthy TD, Karellas P, Henderson SA, Giannis M, O'Keefe DF, Heery G, et al. Dendrimers as drugs: discovery and preclinical and clinical development of dendrimer-based microbicides for HIV and STI prevention. *Molecular Pharmaceutics*. 2005;2(4):312-8.
5. Witvrouw M, Fikkert V, Pluymers W, Matthews B, Mardel K, Schols D, et al. Polyanionic (i.e., polysulfonate) dendrimers can inhibit the replication of human immunodeficiency virus by interfering with both virus adsorption and later steps (reverse transcriptase/integrase) in the virus replicative cycle. *Molecular Pharmacology*. 2000;58(5):1100-8.
6. Bernstein DI, Stanberry LR, Sacks S, Ayisi NK, Gong YH, Ireland J, et al. Evaluations of unformulated and formulated dendrimer-based microbicide candidates in mouse and guinea pig models of genital herpes. *Antimicrobial Agents & Chemotherapy*. 2003;47(12):3784-8.
7. Bourne N, Stanberry LR, Kern ER, Holan G, Matthews B, Bernstein DI. Dendrimers, a new class of candidate topical microbicides with activity against herpes simplex virus infection. *Antimicrobial Agents & Chemotherapy*. 2000;44(9):2471-4.
8. Jiang YH, Emau P, Cairns JS, Flanary L, Morton WR, McCarthy TD, et al. SPL7013 gel as a topical microbicide for prevention of vaginal transmission of SHIV89.6P in macaques. *AIDS Research & Human Retroviruses*. 2005;21(3):207-13.
9. Dezzutti CS, James VN, Ramos A, Sullivan ST, Siddig A, Bush TJ, et al. In vitro comparison of topical microbicides for prevention of human immunodeficiency virus type 1 transmission. *Antimicrobial Agents & Chemotherapy*. 2004;48(10):3834-44.
10. Cummins J, Abner SR, Morken T. Human cervical and colorectal explants for safety and efficacy testing of topical microbicides. *Microbicides 2004*. London, UK; 2004.
11. Abner SR, Guenthner PC, Guarner J, Hancock KA, Cummins JE, Jr., Fink A, et al. A human colorectal explant culture to evaluate topical microbicides for the prevention of HIV infection. *Journal of Infectious Diseases*. 2005;192(9):1545-56.
12. Starpharma PL. Investigator's Brochure: SPL7013 Gel (VivaGel®) Version CIB-001-07; 2008.

13. Patton DL, Cosgrove Sweeney YT, McCarthy TD, Hillier SL. Preclinical safety and efficacy assessments of dendrimer-based (SPL7013) microbicide gel formulations in a nonhuman primate model. *Antimicrobial Agents & Chemotherapy*. 2006;50(5):1696-700.
14. Noveon I. Bulletin 14: Formulating Topical Properties. http://www.pharmalubrizol.com/Bulletins/epb14pdf#xml=http://www.homecare.noveon.com/cgi_bin/texisexe/webinator/search/xmltxt?query=Formulating+Topical+Properties&pr=Lubrizol&prox=page&rorder=500&rprox=500&rdfreq=500&rwfreq=500&rlead=500&sufs=0&order=r&cq=&id=4798420b19.
15. Noveon I. Toxicology/Regulatory/Health, Safety & Environmental Studies of Powdered Carbopol® Polymers. <http://www.homecare.noveon.com/Toxicology/TOX-006pdf>. pdf 2006 March 2001.
16. Cummins JE, Jr., Guarner J, Flowers L, Guenther PC, Bartlett J, Morken T, et al. Preclinical testing of candidate topical microbicides for anti-human immunodeficiency virus type 1 activity and tissue toxicity in a human cervical explant culture. *Antimicrobial Agents & Chemotherapy*. 2007;51(5):1770-9.
17. Panel CIRE. Final Assessment Report of the Safety of Carbomers -934, -910, -934P, -940, -941, and -962. *Journal of the American College of Toxicology*. 1982;1(2):109-41.
18. CONRAD. Investigator's Brochure: Universal Placebo Gel. 2005;Ver. 1.0.
19. Tien D, Schnaare RL, Kang F, Cohl G, McCormick TJ, Moench TR, et al. In vitro and in vivo characterization of a potential universal placebo designed for use in vaginal microbicide clinical trials. *AIDS Res Hum Retroviruses*. 2005 Oct;21(10):845-53.
20. Patty's Industrial Hygiene and Toxicology Online. <http://www3.interscience.wiley.com/cgi-bin/mr/home/104554795/HOME>. accessed 4/20/06.
21. Guttner J, Klaus S, Heinecke H. Embryotoxizität intraperitoneal applizierter Hydroxyethylcellulose bei der Maus. *Anatomischer Anzeiger*. 1981;149(3):282-5.
22. Schwartz JL, Ballagh SA, Kwok C, Mauck CK, Weiner DH, Rencher WF, et al. Fourteen-day safety and acceptability study of the universal placebo gel. *Contraception*. 2007;75(2):136-41.
23. Dreisbach RH. *Handbook of Poisoning*. 9 ed. Los Altos, California: Lang Medical Publications; 1977.
24. Barnhart KT, Pretorius ES, Timbers K, Shera D, Shabbout M, Malamud D. Distribution of a 3.5-mL (1.0%) C31G vaginal gel using magnetic resonance imaging. *Contraception*. 2005;71(5):357-61.

Section 3. Documentation Requirements

Study staff is responsible for proper collection, management, storage, quality control, and quality assurance of all study-related documentation. This section contains information on the Essential Documents that each study site must maintain throughout the study. It also contains information related to establishing adequate and accurate participant research records — commonly referred to as participant “case history records” — for MTN 004.

3.1 Essential Documents

The Division of AIDS (DAIDS) Policy *Requirements for Essential Documents in DAIDS Funded and/or Sponsored Clinical Trials* (The Division of AIDS (DAIDS) Standard Operating Procedures (SOPs) for Essential Documents and Source Documentation) specifies the essential documents that study sites must maintain for DAIDS-sponsored studies, including MTN 004. When required documents are modified or updated, the original and all modified or updated versions must be maintained. Although all required documentation must be available for inspection at any time, all documents need not be stored together in one location.

Section Appendix 3-1 presents a suggested essential documents filing structure for MTN 004. Study sites are not required to adopt the suggested structure, but are encouraged to consider it when developing their filing approach for MTN 004. Study sites also are encouraged to establish an SOP to document their filing approach. Further clarifications of the suggested filing structure are as follows:

- Essential documents may be stored in files and/or in binders. The files/binders listed in Section Appendix 3-1 may be further subdivided, consolidated, and/or re-organized if desired.
- It is recommended that a contents sheet be maintained and inserted as the first page(s) of each file/binder. Within each file/binder, it is recommended that documents be filed in ascending date order (most recent documents in front).
- To preserve blinding, certain documents related to the investigational study products will be stored in site pharmacies. A listing of essential documents to be maintained in the pharmacies is provided in Section 3.4, rather than Section Appendix 3-1.
- To facilitate routine inspection by study monitors, certain laboratory-related essential documents should be stored in the main study essential documents files/binders (see items 26-28 in Section Appendix 3-1). Other lab-related essential documents (e.g., lab SOPs) may be filed in the site’s laboratory files.
- The suggested filing structure assumes that MTN 004 participant case history records will be stored separately from the other essential documents listed in Section Appendix 3-1. Section 3.3 below provides information on the required contents of these records. The suggested filing structure also assumes that the MTN 004 Screening and Enrollment Log, Participant Name-ID Number Link Log, Clinic Randomization Envelope Tracking Record, and Replacement Envelope Tracking Record (which are described in Section 4 of this manual) will be stored in the study clinic or data management area, and not necessarily with the other essential documents listed in Section Appendix 3-1.

- For the ATN sites: The Protocol Registration Policy of the Pediatric, Adolescent, and Maternal AIDS Branch (PAMAB) of the National Institute of Child Health and Human Development (NICHD) for MTN-004 Study in Section Appendix 3-8.
- For the MTN site: The DAIDS Protocol Registration Policy and Procedure Manual located at: <http://rcc.tech-res.com/forms.htm>.

3.2 Site Activation Requirements

After study sites have received final approval from their local Institutional Review Boards (IRB), they must submit protocol registration materials. The ATN sites will complete protocol registration with the National Institute of Child Health and Human Development (NICHD) via Westat. The MTN site will complete protocol registration with the DAIDS RCC Protocol Registration Office. For the ATN sites, when the Data and Operations Center (DOC) at Westat has received all required registration materials, and met all other activation requirements, the DOC will approve the site's protocol registration and notify the site that it may begin protocol enrollment. When the MTN site has obtained protocol registration approval and met all other activation requirements, the MTN CORE (FHI) will notify the site that it may begin protocol enrollment. Protocol registration must occur before any site can enroll any participants into the study.

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair, NIAID Medical Officer, and NICHD Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s), and where necessary, submitted by Starpharma to the FDA, prior to implementing the amendment.

3.3 Participant Case History Documents

Study sites must maintain adequate and accurate participant case history records containing all information pertinent to MTN 004 for each study participant.

3.3.1 Case History Contents

Participant case histories should contain all of the following elements:

- Basic participant identifiers.
- Documentation that the participant provided written informed consent to screen for and participate in the study prior to the conduct of any screening or study procedures, respectively.
- Documentation that the participant met the study's selection (eligibility) criteria.
NOTE: For participants with a vasectomized partner, self report of vasectomy will be sufficient documentation to meet the contraceptive use eligibility criterion.
- A record of the participant's random assignment.
- A record of the participant's exposure to the investigational study products.

- A record of all contacts, and attempted contacts, with the participant.
- A record of all procedures performed by study staff during the study.
- Study-related information on the participant's condition before, during, and after the study, including:
 - Data obtained directly from the participant (e.g., interview responses and other self-reported information)
 - Data obtained by study staff (e.g., exam and lab findings)
 - Data obtained from non-study sources (e.g., non-study medical records)

In addition to the above, DAIDS requires that all protocol events (departures/deviations/violations) be documented in participant records, along with reasons for the events and measures taken to prevent or correct them, if applicable.

Note: In addition to documenting all protocol departures/deviations/violations on site, MTN 004 study sites also must report protocol events to DAIDS and others per the MTN MOP, Section 15-4, which can be found at the following web site:

<http://www.mtnstopshiv.org/node/187>

3.3.2 Concept of Source Data and Source Documentation

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines the terms source data and source documentation as follows:

Source data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents: Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, colposcopic images, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the trial, and any other relevant documents that may be considered as participant data or records).

Source documents are commonly referred to as the documents —paper-based or electronic— upon which source data are first recorded. All study sites must adhere to the standards of source documentation specified in the DAIDS SOP for Source Documentation which can be found at <http://www3.niaid.nih.gov/research/resources/DAIDSCLinRsrch/Regulatory.htm>). The DAIDS policy specifies both requirements and recommendations. Study sites must comply with all requirements and are encouraged, but not required, to comply with all recommendations.

For MTN 004, it is expected that participant case history records will consist of the following source documents:

- Narrative chart notes
- Clinic randomization envelopes, replacement envelopes, and prescriptions documenting participants' random assignments
- Study Gel Request Slips, Study Gel Re-supply Worksheets, Participant Replacement Assessment Worksheets
- Visit checklists
- Local laboratory testing logs and result reports
- DataFax and Non-DataFax forms provided by the MTN Statistical and Data Management Center (SDMC)
- Colposcopic images
- Other source documents (e.g., site-specific worksheets, non-study medical records)

As a condition for study activation, each study site must establish an SOP for source documentation that specifies the use of the above-listed documents as source documents. Although it is the responsibility of each site to determine the most appropriate source document for each required case history element, Section Appendix 3-2 provides a guide that sites may follow for this study. Supplemental information on the use of chart notes, visit checklists, and forms provided by the MTN SDMC is provided below. Detailed information on proper completion, maintenance, and storage of participant randomization and product dispensing documentation is provided in Sections 4, 6, and 9 of this manual. Detailed information on proper completion of DataFax and Non-DataFax forms provided by the MTN SDMC is provided in Section 14 of this manual.

Chart Notes: Study staff must document every contact with a study participant in a signed and dated chart note specifying the date, type, purpose, and location of the contact, and the general status of the participant. The time and location at which a contact takes place, as well as which particular procedures take place, should be specified when necessary to document adherence to protocol requirements. Chart notes also must be used to document the following:

- The screening and enrollment informed consent processes (see also Section 5)
- Procedures performed that are not recorded on other source documents
- Pertinent data about the participant that are not recorded on other source documents
- Protocol events that are not otherwise captured on other source documents

Study sites are strongly encouraged to adopt a common format — such as the Subjective-Objective-Assessment-Plan (SOAP) format — for all chart notes, to help ensure adequacy and consistency of note content and maximize adherence to GCP standards. Several sample notes in SOAP format are provided in Section Appendix 3-3.

Visit Checklists: The checklists in Section 7 of this manual represent convenient tools to fulfill the requirement of documenting all study procedures performed with each study participant. Note, however, that checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to document procedures performed at unscheduled study visits, and/or to explain why procedures in addition to those listed on a checklist may have been performed or why procedures listed on a checklist were not performed. Chart notes also may be required to document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements).

DataFax and Non-DataFax Forms Provided by the MTN SDMC: The case report forms for this study are designed for use with the DataFax data management system described in Section 14 of this manual. The SDMC will provide these forms to each site. The SDMC also will provide several study-specific non-DataFax forms to each site. See Section Appendix 3-4 for a listing of all DataFax and non-DataFax forms to be provided for this study.

For each site, forms that are administered directly to participants will be available in local languages relevant to the site. The SDMC will provide each site with Screening files (containing Screening and Enrollment Visit forms) and Participant Study Notebooks (with separate visit tabs containing the forms needed for a given participant and study visit). As shown in Section Appendices 3-5 and 3-6, many of the DataFax and non-DataFax forms provided by the SDMC have been designed to serve as source documents. Before the study starts, each study site must identify the forms that routinely will be used as source documents in its SOP for source documentation, and must follow the specifications of this SOP consistently for all study participants. In the event that study staff is not able to record data directly onto forms designated as source documents per the site Source Documentation SOP, the following procedures should be undertaken:

- Record the data onto an alternative source document
- Enter the alternative source document into the participant's study chart
- Transcribe the data from the alternative source document onto the appropriate form
- Enter a chart note stating the relevant study visit date and the reason why an alternative source document was used

3.3.3 Document Organization

All information pertaining to the participants (including a case history) must be stored in the same manner for all study participants. Study staff must store all study records securely and confidentially in areas with access limited to authorized study staff only (see Protocol Section 13.5 Participant Confidentiality). Study staff is responsible for purchasing file folders, binders, storage cabinets, and any other equipment or supplies needed to properly store all records.

Study-related documentation collected during the screening process should be stored in file folders or thin notebooks for each potential participant. All screening documentation — for potential participants who eventually enroll in the study as well as for those who do not enroll — must be maintained and available for monitoring throughout the study. For participants who enroll in the study, screening documentation (from successful screening attempt that led to enrollment *only*) should be transferred into SDMC-provided participant notebooks, which will serve as participants' study notebooks for the duration of their participation in the study.

All documents contained in participant case history records must bear a participant identifier, which generally will consist of either the participant identification number (PTID) or the participant name. To maximize participant confidentiality, the PTID should be used whenever possible, and records that bear names or other personal identifiers, such as locator forms and informed consent forms, should be stored separately from records identified by PTID. Any documents transferred or transmitted to a non-study site location — including DataFax forms and Expedited Adverse Event Forms — must be identified by PTID only.

Regardless of whether the identifier on a particular document consists of the participant name or PTID, the original identifier may not be obliterated or altered in any way, even if another identifier is added. When necessary to maintain confidentiality, identifiers may be obliterated on copies of original source documents. For example, if medical records obtained from a non-study health care provider bear the participant's name, the original documents bearing the name must be stored unaltered with other study documents bearing the name. However, a copy of the original documents could be made, the PTID could be entered onto the copies, and then the participant name could be obliterated from the copies. Copies handled in this way could then be stored in participants' study notebooks and/or transferred or transmitted to the DAIDS and NICHD Medical Officers.

Copies of source documents may not be transferred to any other non-study site location without prior authorization from the DAIDS and NICHD Medical Officers or the CORE (FHI) Clinical Research Manager (or their designees).

All on-site databases must be secured with password-protected access systems. Any lists, logbooks, appointment books, or other documents that link PTIDs to other participant identifiers must be stored securely in a location separate from records identified by either participant name only or PTID only. When in use, these documents must not be left unattended or otherwise accessible to study participants, other study clinic patients, or any other unauthorized persons.

As a condition for study activation, each study site must establish an SOP for data management. This SOP minimally should contain the following elements:

- Procedures for assigning PTIDs, linking PTIDs to participant names, and storing the name-PTID link log
- Procedures for establishing participant files/charts/notebooks
- During-visit participant chart and case report form review procedures
- Post-visit participant chart and case report form review procedures and timeframes
- Data transmission procedures, including timeframes, case report form storage locations before and after faxing, and mechanisms for identifying when forms have been transmitted
- Procedures for resolving data quality control notes from the SDMC

- Procedures for handling and filing field workers' logs, worksheets, etc.
- Storage locations for blank case report forms
- Storage locations for documents identified by participant names or other personal identifiers
- Storage locations for documents identified by PTID
- Procedures for back up of electronic study data (if applicable)
- Handling of participant study records for off-site contacts and visits
(*Note: For MTN 004, study visits may **not** be conducted off-site*)
- Confidentiality protections
- Other ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

3.4 Study Product Accountability, Chain of Custody, and Dispensing Documentation

The following essential documents should be maintained in study site pharmacies:

- Current MTN 004 protocol
- Current Investigator's Brochure (IB) VivaGel™ (if IB on file in the clinic essential document files are not easily accessible to pharmacy staff)
- Current MTN 004 FDA Form 1572
- Current list of authorized prescribers and staff authorized to sign MTN 004 Study Product Request Slips (names and signatures)
- Pharmacy Establishment Plan
- MTN 004 pharmacy and product-related SOPs
- MTN 004 PTID list (provided by the MTN SDMC)
- MTN 004 product shipping and receipt documentation
- MTN 004 product storage temperature logs
- MTN 004 investigational agent accountability records
- MTN 004 participant-specific records (including prescriptions, product re-supply slips, dispensing records, and DataFax forms as applicable)
- MTN 004 monitoring visit reports
- MTN 004 communications with site clinic staff
- MTN 004 communications with the MTN CORE Pharmacist and Brecon
- MTN 004 communications with the MTN Coordinating and Operations Center (CORE)
- MTN 004 communications with the MTN SDMC
- Other MTN 004 communications
- Other locally-required administrative, operational, and/or regulatory documentation
- MTN 004 drug destruction log or return shipment log

Pharmacy staff will document the receipt, dispensing, and final disposition of the investigational products used in the study (i.e., VivaGel™, VivaGel™ placebo gel, and HEC placebo gel).

Pharmacy staff also will maintain in the study pharmacies Participant-Specific Pharmacy Dispensing Records containing information on product dispensations for all enrolled participants. Study clinic staff will contribute to the documentation of product dispensation and chain of custody as described in Sections 4, 6, and 9 of this manual.

The specifications related to document security and participant confidentiality described in Section 3.3.3 also apply to records maintained in the study pharmacies. All records must be stored securely in the pharmacies with access limited to authorized study pharmacy staff only.

To preserve the blinding of all protocol team members to participants' random assignments to study gel (VivaGel™, VivaGel™ placebo gel or HEC placebo gel), neither the study clinic staff, study participants, nor the MTN 004 team members will be provided access to product-related documentation maintained in the study pharmacies. Pharmacy staff may provide copies of some participant-specific documentation maintained in the study pharmacies (e.g., chart notes) to clinic staff for purposes of communication and operational coordination. However, decisions to provide such documentation to clinic staff will be made by pharmacy staff only, and under no circumstances will documentation released from the pharmacy include participants' product dispensing records.

Note: Double blinding of non-pharmacy site staff will only pertain to random assignment, and not frequency of study gel use. All site study staff will remain unblinded to participants' frequency of study gel use.

3.5 Record Retention Requirements

All records must be retained on-site throughout the study's period of performance. In accordance with U.S. regulations, all study records will be retained until NICHD, DAIDS and Starpharma give approval for record destruction. Study product records must be stored in the study pharmacies, with access limited to authorized study pharmacy staff only, until the study is unblinded. DAIDS will provide further instructions for long-term storage of study records after the study is completed.

Section Appendix 3-1
Suggested Filing Structure for MTN 004 Essential Documents

<p>File/Binder #1: MTN 004 Protocol and Current Informed Consent Forms</p> <ol style="list-style-type: none"> 1. MTN 004 Protocol (including copy of signed and dated protocol signature page): Version 1.0, 2.0 and 3.0 and any subsequent protocol Clarification Memos, Letters of Amendment, and Amendments 2. Currently-approved MTN 004 informed consent forms
<p>File/Binder #2: Regulatory Authority Documentation (if applicable)</p> <ol style="list-style-type: none"> 3. Regulatory Authority Correspondence/Authorization/Approval/Notification of Protocol (if applicable; if more than one regulatory authority has oversight responsibility for research performed at the study site, include subsections for each authority)
<p>File/Binder #3A: IRB/EC Documentation for [IRB/EC A]</p> <ol style="list-style-type: none"> 4. FWA documentation for IRB/EC A 5. Roster of IRB/EC A (if available) 6. Relevant IRB/EC A Submission Requirements/Guidelines/SOPs 7. IRB Correspondence for IRB/EC A: File complete copies of all correspondence to and from the IRB/EC; include all enclosures/attachments for all submissions, even if copies of the enclosures/attachments are filed elsewhere; include all approval documentation.
<p>File/Binder #3B: IRB/EC Documentation for [IRB/EC B]</p> <ol style="list-style-type: none"> 8. FWA documentation for IRB/EC B 9. Roster of IRB/EC B (if available) 10. Relevant IRB/EC B Submission Requirements/Guidelines/SOPs 11. IRB Correspondence for IRB/EC B: File complete copies of all correspondence to and from the IRB/EC; include all enclosures/attachments for all submissions, even if copies of the enclosures/attachments are filed elsewhere; include all approval documentation.
<p>File/Binder #4: Product Safety Information</p> <ol style="list-style-type: none"> 12. Investigator's Brochure for VivaGel gel: current version and any subsequent updates 13. Product Safety Information/Reports/Memos <p>Notes:</p> <ul style="list-style-type: none"> • It is assumed that expedited adverse event reports will be stored in participant study notebooks. • It is assumed that documentation of IRB/EC submission of above-listed documents (if applicable) will be maintained in the relevant IRB/EC Files/Binders (i.e., File/Binder #3A and #3B).
<p>File/Binder #5: MTN 004 Study-Specific Procedures (SSP) Manual</p> <ol style="list-style-type: none"> 14. Final version 1.0 and any subsequent updates <p>Notes:</p> <p>For this reference copy of the SSP Manual, do not discard out-dated pages or sections when updates are issued; retain all versions of all pages as a complete historical record.</p> <ul style="list-style-type: none"> • The SSP Manual contains reference versions of all study case report forms, therefore additional (blank) copies of the case report forms need not be stored elsewhere in the essential document files.
<p>File/Binder #6: MTN 004 Study-Specific Standard Operating Procedures</p> <ol style="list-style-type: none"> 15. Final approved version of each SOP, and any subsequent updates to each

Section Appendix 3-1
Suggested Filing Structure for MTN 004 Essential Documents

<p>File/Binder #7: MTN 004 Staffing Documentation</p> <p>16. FDA Form 1572 (the original form should be submitted to Starpharma a copy of the form submitted for Protocol Registration, and any subsequent updates)</p> <p>17. MTN 004 Investigator of Record CV (copy of CV submitted for Protocol Registration; ensure that the CV is current prior to initiating MTN 004; it is recommended that CVs be signed and dated to document at least annual updating)</p> <p>18. Financial Disclosure Forms (original signed and dated forms, and any subsequent updates)</p> <p>19. Study Staff Roster (copies submitted to Westat, if applicable, and FHI for study activation, and any subsequent updates)</p> <p>20. Study Staff Identification and Signature Sheet (if not combined with staff roster; copies and any subsequent updates)</p> <p>21. Study Staff Delegation of Duties (if not combined with staff roster; copies and all updates)</p> <p>22. CVs for Study Staff other than the IoR (ensure that all CVs are current prior to initiating MTN 004; it is recommended that CVs be signed and dated to document at least annual updating)</p> <p>23. Study Staff Job Descriptions</p> <p>24. Documentation of Study Staff Training</p>
<p>File/Binder #8: Local Laboratory Documentation</p> <p>25. Local Laboratory Certification(s), Accreditation(s) and/or Validation(s): file documentation current at time of study activation and all subsequent updates</p> <p>26. Local Laboratory Normal Ranges: file documentation of relevant normal ranges for all protocol-specified tests current at time of study activation and all subsequent updates</p> <p>27. Laboratory Manager CV (or cross-reference to CV contained in File/Binder #7)</p> <p>Note:</p> <ul style="list-style-type: none"> • It is recommended that a cross-reference be included in this file/binder specifying the storage location(s) of other lab-related essential documents filed in the local lab(s).
<p>File/Binder #9: Monitoring Visit Documentation</p> <p>28. Monitoring Visit Log</p> <p>29. Initiation and Monitoring Visit Reports and Documentation of Response to Visit Findings</p>
<p>File/Binder #10: Documentation of Other MTN Site Visits</p> <p>30. (Non-Monitoring) Site Visit Log</p> <p>31. MTN CORE Site Visit Reports and Documentation of Response to Visit Findings</p> <p>32. MTN SDMC Site Visit Reports and Documentation of Response to Visit Findings</p> <p>33. MTN Network Lab Site Visit Reports and Documentation of Response to Visit Findings</p> <p>34. Other Site Visit Reports and Documentation of Response to Visit Findings</p>
<p>File/Binder #11: Study-Related Sponsor Communications</p> <p>35. Study-Related Communications to and from DAIDS</p> <p>36. Study-Related Communications to and from NICHD</p> <p>Notes:</p> <ul style="list-style-type: none"> • Communications should be filed beginning from the date of the MTN 004 site specific Training. • Communications related to individual MTN 004 study participants will be filed in individual participant study records. • As needed to preserve blinding, product-related communications will be stored in the study pharmacy.

Section Appendix 3-1
Suggested Filing Structure for MTN 004 Essential Documents

<p>File/Binder #12: Other Study-Related Communications</p> <p>37. Study-Related Communications to and from MTN CORE 38. Study-Related Communications to and from MTN SDMC 39. Study-Related Communications to and from MTN Network Lab 40. Other Study-Related Communications</p> <p>Notes:</p> <ul style="list-style-type: none"> • Communications should be filed beginning from the date of the MTN 004 site specific training. • Communications related to individual MTN 004 study participants will be filed in individual participant study records. • As needed to preserve blinding, product-related communication will be stored in the study pharmacy.
<p>File/Binder #13: Study Site Staff Meeting Documentation</p> <p>41. MTN 004 Staff Meeting Agendas, Participant Lists/Sign-In Sheets, and Summaries</p> <p>Note:</p> <ul style="list-style-type: none"> • Meeting documentation should be filed beginning from the date of the MTN 004 site specific training.
<p>File/Binder #14: Conference Call Documentation</p> <p>42. MTN 004 Protocol Team Conference Call Summaries 43. Summaries of Other MTN 004 Conference Calls</p> <p>Note:</p> <ul style="list-style-type: none"> • Conference call summaries will be filed beginning from the date of the MTN 004 site specific training.
<p>File/Binder #15: DAIDS and Other Reference Documentation</p> <p>44. DAIDS Policy <i>Requirements for Source Documentation at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials</i> (Version 2.0 and any subsequent updates) 45. DAIDS Policy <i>Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials</i> (Version 2.0 and any subsequent updates) 46. ATN sites: The Protocol Registration Policy of the Pediatric, Adolescent, and Maternal AIDS Branch (PAMAB) of the National Institute of Child Health and Human Development (NICHD) for the MTN 004 Study (Version 0.5, February 2007 and any subsequent updates) 47. MTN sites: DAIDS Protocol Registration Policy and Procedures Manual (August 2004 and any subsequent updates) 48. Manual for Expedited Reporting of Adverse Events to DAIDS 49. US Regulations Applicable to Conduct of MTN 004 (45 CFR 46; 21 CFR 50, 54, 56, and 312) 50. Any other relevant manuals or reference documents</p>
<p>File/Binder #16: Site-Specific Study Activation Documentation</p> <p>50. Site-Specific Study Activation Documents</p>

Section Appendix 3-2
Guide to Required Case History Elements and Source Documents for MTN 004

Required Case History Element	Source Documents*
Basic participant identifiers.	Locator form; Demographics forms.
Documentation that the participant provided written informed consent to screen for and participate in the study.	Signed and dated informed consent forms; signed and dated chart notes stating that informed consent was obtained prior to initiating study procedures.
Documentation that the participant met the study selection (eligibility) criteria.	Demographics form, locator form; Screening 1 Visit Eligibility form (non-DataFax); Screening 2 Visit/Enrollment Eligibility form (non-DataFax), Screening Summary (non-DataFax); Clinical Eligibility form (non-DataFax); Safety Laboratory Results form; STI Laboratory Results form; (non-DataFax) Baseline Medical History form; Concomitant Medications Log form; Physical Exam form (non-DataFax); Screening 1 and Enrollment Pelvic Exam form; Screening 2 Pelvic exam form (if indicated); (non-DataFax) Pelvic Exam Diagrams; Pelvic Laboratory Results form; Enrollment form; Pre-Existing Conditions form; local lab logs and result reports [§] ; signed and dated chart notes.
A record of the participant's random assignment.	MTN 004 prescription or MTN 004 replacement prescription; MTN 004 Participant-Specific Pharmacy Dispensing Record; Enrollment form; dispensed gel chain of custody logs.
A record of the participant's exposure to the investigational study products.	MTN 004 Gel Re-Supply Worksheet, MTN 004 Study Gel Request Slip, MTN 004 Participant-Specific Pharmacy Dispensing Record; dispensed gel chain of custody logs, visit checklists.
A record of all contacts, and all attempted contacts, with the participant.	Signed and dated chart notes, and/or other worksheets or site-specific documents if designated in site SOPs.
A record of all procedures performed by study staff.	Completed visit checklists; signed and dated chart notes detailing (i) procedures performed in addition to those contained on the checklist and/or (ii) the reason why procedures contained on the checklist were not performed.

Section Appendix 3-2 continued
 Guide to Required Case History Elements and Source Documents for MTN 004

<p>Information on the participant's condition before, during, and after the study.</p>	<p>All documents listed above; Family Planning Methods form, Study Gel Adherence form; Acceptability Assessment form; (non-DataFax) Follow-up Medical History form; Genital Bleeding Assessment; Follow-up Pelvic Exam form; (non-DataFax) Pelvic Exam Diagrams; (non-DataFax) History of Genital Symptoms form; Baseline Genital Symptoms form; Follow-up Genital Symptoms form; Pharmacokinetics form; Pelvic Laboratory Results form; Safety Laboratory Results form; STI Laboratory Results form; HSV-2 Culture form; Adverse Experience Log form; HIV Test Results form; Product Hold/Discontinuation form; Pregnancy Report and History form; Pregnancy Outcome form; Missed Visit form; Follow-Up Visit form; Interim Visit form; End of Study Inventory form; local lab logs and result reports from the local lab[§]; results of information pertinent to the study obtained from non-study sources; signed and dated chart notes.</p>
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*Other site-specific source documents also may be used.

§A clinician must review all local laboratory reports and document this review by signing and dating all reports.

Section Appendix 3-3
Sample Chart Notes for MTN 004 in Subjective-Objective-Assessment-Plan (SOAP) Format

<p>Sample Chart Note for a Screening Visit: 15 AUG 2008: Participant presented for MTN 004 screening. Obtained written informed consent for screening before initiating any procedures. Procedures were completed per protocol, visit checklist and SOPs. S: Participant reported no current health problems. O: Pregnancy test negative, participant behaviorally eligible per the Screening Eligibility form, HIV test sent to lab. A: Participant is eligible for the study thus far. P: Screening visit 2 and Enrollment scheduled for 01 SEP 2008. { staff signature }</p>
<p>Sample Chart Note for a Screening Visit: 15 AUG 2008: Participant presented for MTN 004 screening. Obtained written informed consent for screening before initiating any procedures. Procedures were completed per protocol, SOPs and visit checklist, with the additions listed here. S: Participant complained of current genital itching and yellowish discharge, no other current health problems. O: Participant behaviorally eligible per the Screening 1 Visit Eligibility form, tested negative for pregnancy HIV test sent to lab. A: Syndromic treatment provided. Participant instructed that she is not eligible to enroll in the study. P: Participant counseled to contact her primary care provider if symptoms do not resolve in 5-7 days. { staff signature }</p>
<p>Sample Chart Note for Screening: 15 AUG 2008: Participant presented for MTN 004 screening. Obtained written informed consent for screening before initiating any procedures. Procedures were completed per protocol, SOPs and the visit checklist, with the additions listed here. S: Participant complained of current genital itching and yellowish discharge. O: Participant behaviorally eligible per the Screening 1 Visit Eligibility form, tested negative for pregnancy, and HIV test sent to lab. Pelvic exam completed to assess genital symptoms. Discharge noted, but no abdominal tenderness or other signs present. Wet prep was positive for trichomonads, negative for whiff test, clue cells, and yeast. A: Treatment provided. Participant instructed that she is not eligible to enroll in the study. P: Participant counseled to contact her primary care provider if symptoms do not resolve in 5-7 days. { staff signature }</p>

Section Appendix 3-3 continued
Sample Chart Notes for MTN 004 in Subjective-Objective-Assessment-Plan (SOAP) Format

Sample Chart Note for Enrollment:

29 AUG 2008: Participant presented for MTN 004 Enrollment visit. Procedures completed per protocol, visit checklist and SOPs. Participant was confirmed eligible and willing to take part in study. Written informed consent obtained for enrollment before initiating any study procedures. Participant was not willing to consent to specimen storage for possible future research.

S: Participant reported no genital symptoms since last visit (screening).

O: Screening 1 Visit GC and CT tests were negative. Today's pregnancy test was negative. Pelvic exam and wet mount were normal (see findings on DataFax forms). Participant behaviorally eligible per Screening 1 Visit and Screening 2 Visit/Enrollment Eligibility form. Screening documentation reviewed and eligibility confirmed by [insert name]. {counter-signature }

A: Participant is eligible for the study.

P: Participant was enrolled in study. Week 1 visit scheduled for 05 SEP 2008.
{ staff signature }

Sample Chart Note for Enrollment Visit:

29 AUG 2008: Participant presented for MTN 004 Enrollment visit. Procedures completed per protocol, SOPs and visit checklist. Enrollment procedures were discontinued at this visit due to participant ineligibility.

S: Participant reported no current health problems.

O: Screening 1 GC and CT lab tests were negative, but today's pregnancy test was positive. Enrollment discontinued upon finding this result.

A: Participant is pregnant — not eligible for study.

P: Participant informed that she is pregnant and referred to [clinic name] for antenatal care. Participant informed that she can return to find out about study participation when she is no longer pregnant.

{ staff signature }

Sample Chart Note for Follow-up Visit:

04 SEP 2008: Participant presented for MTN 004 at Week 1 visit. Procedures completed per protocol, visit checklist and SOPs.

S: No issues/problems reported since last visit.

O: Pregnancy test negative.

A: No issues of concern.

P: Week 2 visit scheduled for 11 SEP 2008.
{ staff signature }

Section Appendix 3-4
MTN 004 DataFax and Non-DataFax Forms

MTN 004 DataFax Forms	MTN 004 Non-DataFax Forms
Screening Consent	Screening 1 Visit Eligibility
Demographics	Screening 2 Visit/Enrollment Eligibility
Pharmacokinetics	Follow-up Medical History
Screening 1 and Enrollment Pelvic Exam	Baseline Medical History
Screening 2 Pelvic Exam	History of Genital Symptoms
Follow-up Pelvic Exam	Screening Summary
Enrollment	Pelvic Exam Diagrams
STI Laboratory Results	Clinical Eligibility
Pelvic Laboratory Results	Physical Exam
Safety Laboratory Results	
HSV-2 Culture	
HIV Test Results	
Pre-Existing Conditions	
Concomitant Medications Log	
Baseline Genital Symptoms	
Follow-up Genital Symptoms	
Follow-up Visit	
Genital Bleeding Assessment	
Family Planning Methods	
Study Gel Adherence	
Acceptability Assessment	
Product Hold/Discontinuation	
Adverse Experience Log	
Pregnancy Report and History	
Pregnancy Outcome	
Interim Visit	
Missed Visit	
CASI Tracking	
Termination	
End of Study Inventory	

Section Appendix 3-5
Use of MTN 004 DataFax Forms as Source Documents

Form Name	Acronym	Source?	Comments
Screening Consent	SC-1	[No]	Form [may be] source for item 1. Items 2 and 2a are based on source data recorded in participant chart notes and on participant informed consent forms.
Demographics	DEM-1	Yes	Form is interviewer-administered; participant responses are recorded directly onto the form.
STI Laboratory Results	SLR-1	[No]	Items 1f-3b1 require local lab documentation as source. Items 4a-4b require central lab documentation as source. For items 1a-1e, form may serve as source in cases where results are not documented on a local lab report, but are recorded directly onto the form. Otherwise, the local laboratory report may serve as source.
Safety Laboratory Results	SL-1-2	[Mixed]	Local laboratory report is source for items 1-5b. Form may be source for item 6.
HSV-2 Culture	HSR-1	No	Local laboratory report is source.
Screening 1 and Enrollment Pelvic Exam	SPE-1,2	[Yes]	[It is expected that this form routinely will serve as a source document, with supplemental information recorded on the Pelvic/Colposcopy Diagrams, and in participant chart notes if needed. If, instead, other documents such as participant chart notes routinely will serve as the source document for pelvic exam information, this should be specified.]
Screening 2 Pelvic Exam	RSP-1	[Yes]	[It is expected that this form routinely will serve as a source document, with supplemental information recorded on the Pelvic/Colposcopy Diagrams, and in participant chart notes if needed. If, instead, other documents such as participant chart notes routinely will serve as the source document for pelvic exam information, this should be specified.]
Pelvic Laboratory Results	PLR-1	[Mixed]	For items 1a-1f, form may serve as source in cases where results are not documented on a local lab report, but are recorded directly onto the form. Otherwise, the local laboratory report may serve as source. Local laboratory report is source for item 2.
Baseline Genital Symptoms	BGS-1	Yes	Form is interviewer-administered; participant responses are recorded directly onto the form.
Follow-up Genital Symptoms	FGS-1	Yes	Form is interviewer-administered; participant responses are recorded directly onto the form.

Section Appendix 3-5 (continued)
Use of MTN 004 DataFax Forms as Source Documents

Form Name	Acronym	Source?	Comments
Pre-Existing Conditions	PRE-1	No	All items are based on source data recorded on the Baseline Medical History, Physical Exam, Screening and Enrollment Pelvic Exam forms, Pelvic Exam Diagrams, Baseline Genital Symptoms, and/or participant chart notes.
Concomitant Medications	CM-1	[Yes]	[It is expected that sites will record concomitant medication information directly and initially onto this form, with the exception of family planning/contraceptive use, for which the Baseline Medical History and Follow-up Medical History forms will be source. If instead other documents such as participant chart notes routinely will serve as the source document for this information, then this form is not considered a source document, and the actual source document should be specified here.]
Enrollment	ENR-1	Mixed	Items 1 and 1a are based on source data recorded in participant chart notes and on participant informed consent forms. For items 2, 2b, and 2c, this form may serve as source, or the Clinic Randomization Envelope Tracking Record may serve as source (depending on which is completed first). Items 2a, 2d, and 2e are based on source data recorded on the prescription contained inside the participant's randomization envelope. For item 3, participant chart notes, this form, or the prescription may serve as source. For item 2f the prescription of the participant being replaced serves as source. Items 4-6 are based on source data documented on the Participant-Specific Pharmacy Dispensing Record (stored in the site pharmacy).
Family Planning Methods	FPM-1	No	Responses transcribed from Baseline Medical History form at enrollment and from Follow-up Medical History form during follow-up.
Study Gel Adherence	SGA-1	Yes	Form is interviewer-administered; participant responses are recorded directly onto the form.
Follow-up Visit	FV-1	Mixed	Form may serve as source for item 1 if result is not documented on a local lab report or local log sheet, but is recorded directly onto the form. Form may also serve as source for items 1a, and 3. Participant chart notes and/or AE Log forms are source for items 2-2a. The Participant-Specific Pharmacy Dispensing Record serves as source for items 5-5b.

Section Appendix 3-5 (continued)
Use of MTN 004 DataFax Forms as Source Documents

Form Name	Acronym	Source?	Comments
Follow-up Pelvic Exam	FPE-1-3	[Yes]	[It is expected that this form routinely will serve as a source document, with supplemental information recorded on the Pelvic/Colposcopy Diagrams, and in participant chart notes if needed. If, instead, other documents such as participant chart notes routinely will serve as the source document for pelvic exam information, this should be specified.]
HIV Test Results	HTR-1	[No]	Local laboratory report is source for items 1-4. Local laboratory report and/or form may serve as source for item 5.
Acceptability Assessment	AA-1-5	Yes	Form is interviewer-administered; participant responses are recorded directly onto the form.
Pharmacokinetics	PK-1	[Yes]	Form may serve as source for items 1, 4 and 5. Form may also serve as source for items 2-3 if height and weight are re-assessed at the time of the PK visit, and recorded directly onto this form. The Physical Exam form and/or participant chart notes may also serve as source for items 2-3.
Product Hold/Discontinuation	PH-1	Mixed	Form may be source for all items EXCEPT item 2. Participant chart notes, the PR-1 form, local laboratory report and/or local log sheet, HTR-1 form, and/or AE Log form may serve as source for item 2.
Adverse Experience Log	AE-1	Yes	Form may be source for all items.
Pregnancy Report and History	PR-1	Mixed	Form may be source for item 2. All other items are based on source data recorded on the Baseline and Follow-up Medical History forms.
Pregnancy Outcome	PO-1	Yes	Form may be source for all items if medical records are not available and the data recorded on the form are based on participant self-report.
Genital Bleeding Assessment	GBA-1-3	Mixed	Follow-up Medical History form is source for items 1-3, 12, and 13. Form may be source for items 4-11g, 12a-12b, and 13a-14a. The Adverse Experience Log is source for item 14b.
Interim Visit	IV-1	Mixed	Form may serve as source for items 1-1f, 2a, and 3-4. Form may serve as source for item 2 if result is not documented on a local lab report or local log sheet, but is recorded directly onto the form. The Participant-Specific Pharmacy Dispensing Record serves as source for items 6-6b.
Missed Visit	MV-1	Yes	Form may be source to document that the visit was missed; source data on the reason why the visit was missed also may be recorded on this form.
CASI Tracking	CT-1	Yes	Form may be source for all items.
Termination Form	TM-1	No	All items are based on source data recorded on other documents.
End of Study Inventory	ESI-1	No	All items are based on source data recorded on other documents.

Section Appendix 3-6
Use of MTN 004 Non-DataFax Forms as Source Documents

Form Name	Source?	Comments
Screening 1 Visit Eligibility	Mixed	Screening Informed Consent form is source for item 1. The Screening and Enrollment Log is source for item 2. Form may serve as source for item 3 if documentation of a normal Pap result (in the 12 calendar months prior to screening) is NOT available. Form is source for items 4-25; items are interviewer-administered. Form may be source for item 26 if result is not documented on a local laboratory report or local log sheet, but is recorded directly onto the form. Form may also be source for item 27.
Screening 2 Visit/Enrollment Eligibility	Mixed	Form is source for items 1-13a; items are interviewer-administered. Form may be source for item 14, if result is not documented on a local laboratory report or local log sheet, but is recorded directly onto the form. Form may be source for item 15.
Baseline Medical History	Yes	Form may be source for all items. Data recorded on this form is based on participant self-report, and may also be supplemented with data recorded on other source documents (e.g., non-study medical records).
History of Genital Symptoms	Yes	Form may be source for all items. Data recorded on this form is based on participant self-report, and may also be supplemented with data recorded on other source documents (e.g., non-study medical records).
Physical Exam	Yes	Form may be source for all items.
Pelvic Exam Diagrams	Yes	Form may be source for all items.
Clinical Eligibility	No	All items are based on data recorded on other documents as source.
Screening Summary	No	All items are based on data recorded on other documents as source.
Follow-up Medical History	Yes	Form may be source for all items.

**THE PROTOCOL REGISTRATION POLICY
OF THE PEDIATRIC, ADOLESCENT, AND
MATERNAL AIDS BRANCH (PAMAB)
OF THE NATIONAL INSTITUTE OF CHILD HEALTH
AND HUMAN DEVELOPMENT (NICHD)**

FOR THE

Microbicide Trials Network (MTN) 004 Study

Version 0.5, February 2007

6.1 Background

The Pediatric, Adolescent, and Maternal AIDS Branch (PAMAB—"Program") of the National Institute of Child Health and Human Development (NICHD), as a Branch in a Federal agency (U.S. Department of Health and Human Services—DHHS) that funds clinical research, is responsible for ensuring that the MTN 004 research protocol is conducted in accordance with the Memorandum of Understanding between the MTN and the ATN all governing regulations, policies, and procedures of the DHHS, the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA). PAMAB/NICHD has established this registration policy to meet its responsibility. PAMAB/NICHD has further delegated to the ATN Data and Operations Center (ATN-DOC) the task of collecting, reviewing, and approving the required documentation from the MTN 004 participating sites. Included in this step will be MTN CORE review of each site-specific study informed consent form prior to IRB submission.

This document provides an explanation of the regulatory background for this policy as well as definitions and procedures required for compliance. All sites participating in the MTN 004 study must comply with this policy.

6.2 Federal Regulations

All research funded by NIH must comply with Title 45 Part 46 of the Code of Federal Regulations (45 CFR 46) and the Food and Drug Administration (FDA) 21 CFR 50 (for IND studies).

These documents can be found at <http://www.hhs.gov/ohrp>.

The MTN 004 study must be reviewed by an appropriately constituted institutional review board (IRB) or Ethics Committee (EC) under a Federal-wide assurance (FWA). NICHD must have a record of this

Section Appendix 3-7
The Protocol Registration Policy

review and approval through the ATN-DOC prior to implementation of the protocol. All amendments to the protocol, informed consents, or other study-related documents must be approved by the IRB/EC, and where necessary by Starpharma to the FDA, prior to implementing the amendment.

Information on registering an IRB and obtaining a FWA can also be found at <http://www.hhs.gov/ohrp>.

MTN-funded personnel with questions about general IRB issues should contact NICHD program staff.

6.3 Federal Regulations and Informed Consent

6.3.1 Basic Elements and Appropriate Additional Elements

Basic elements and appropriate additional elements as outlined in 45 CFR § 46.116 and 21 CFR § 50.25 include:

- Statement that the study involves research
- Purposes, duration, and procedures
- Foreseeable risks or discomforts
- Identification of any procedures which are experimental
- Reasonably expected benefits to subject or others
- Disclosure of alternative procedures
- Confidentiality measures
- Compensation, if any, for injury
- Contact people for the study
 - In case of injury
 - For research questions
 - Questions about rights
- Participation is voluntary

Additional elements that the IRB may require:

- Risks to fetus
- Circumstances under which participation may be terminated
- Additional costs to subject
- Consequences of the decision to withdraw

Section Appendix 3-7
The Protocol Registration Policy

- New findings will be provided
- Approximate number of study subjects

6.3.2 MTN 004 Consent Form Templates

The MTN 004 protocol team has provided sample consent forms as appendixes to the MTN 004 study. These sample consent forms are reviewed by NICHD and approved as representing NICHD's assessment of the risk-benefit analysis of the study, and as providing accurate and understandable information to potential subjects and a sound portrayal of study requirements.

For sites that will recruit Spanish-speaking subjects and do not require their own local translations, the ATN-DOC will provide a certified translation of the consent form. This document must be approved by the site's IRB and submitted with registration documents. If the IRB makes changes, the ATN-DOC will request IRB approval of the Spanish consent (indicating that all required elements have been retained) and a letter certifying the translation.

6.3.3 Local Changes to MTN Consent Form Templates

If a site elects or is required by its IRB to delete or make any substantive change to the required elements in the protocol's sample consent, these changes must be highlighted and a written justification from the PI must be included in the registration packet. These changes must be shipped overnight to the ATN-DOC and will be shared with PAMAB/NICHD.

**SUBSTANTIVE CHANGE DOES NOT INCLUDE FORMATTING
ALTERATIONS TO BE CONSISTENT WITH LOCAL IRB PREFERENCE.**

In addition, the minutes of the IRB meeting (or letter from the IRB) must reflect the justification for and the approval of the modifications to the aforementioned sections of the consent form. Consent forms must be the exact consents to be submitted to subjects. There must be no strikeouts in the Informed Consent document. The original IRB approved site consent(s) is to be kept on file at the site.

6.3.4 Subsequent Changes to Previously-Approved Consent Forms

The ATN-DOC must ensure that every consent form used in MTN 004 meets Federal requirements and presents accurate information. Further, the ATN-DOC must have the most current consent form on file. If changes are made to the IRB approved informed consent document **at any time**, the ATN-DOC must receive a copy of the revised IRB approved informed consent with changes highlighted. The ATN-DOC must review and approve the informed consent prior to a site using the document to obtain consent. Consent forms reviewed by the DOC must be the exact consents to be submitted to subjects.

6.4 Continuing Review

The ATN follows HHS regulations in Section 46.019(e), which requires that the IRB review research at intervals appropriate to the degree of risk, but not less than once per year. Sites are responsible for resubmitting their protocols, informed consents, and other supporting documentation to their IRB for continuing review. Once the IRB has approved the continuing research, the site should submit the following to the ATN-DOC:

- MTN 004 Registration Checklist (Exhibit ___)
- New approval from the IRB which includes:
 - Complete protocol title;
 - Protocol/study number and version number;
 - Date of IRB approval;
 - Signature of IRB Chairperson or member designee *;
 - Title of the person signing for the IRB;
 - Expiration data; and
 - Documentation of the IRB/EC designation of a risk/benefit category from 45 CFR 46.404-407.
- New approved consent forms

* Electronic IRB signatures are acceptable as long as the site provides to the DOC a one-time memorandum from the IRB that validates their electronic signature procedure.

If the new consent forms differ significantly from the template, follow the procedure in Sections 6.3.3 and 6.3.4, “Changes to Sample Consent Forms.” Once the DOC receives these records, it will send an acknowledgement of receipt and approval or request for changes.

6.4.1 Sites *May Not* Enroll or See Patients Under a Protocol When IRB Approval has Expired

6.4.2 Sites *May Continue* to see Patients Under a Protocol if the IRB has Approved it but the DOC has Not Yet Confirmed Receipt

6.5 ATN Guidance Documents for Human Subjects Protections for Minors

Site staff preparing study protocol documents for the IRB should always adhere to the requests made in the protocol (e.g., waivers of parental permission or written consent forms). Conversely, no site staff should request a waiver if this waiver is not requested in the protocol itself. The protocol team may always be queried for guidance in these matters.

6.6 Designation of Risk/Benefit Category and Approval of Clinical Studies for Inclusion of Children by Institutional Review Boards/Ethics Committees

For research projects including children or adolescents, the National Institute for Child Health and

Section Appendix 3-7
The Protocol Registration Policy

Human Development (NICHD) requires documentation of the IRB/EC designation of a risk/benefit category from 45 CFR 46.404-407 and IRB/EC approval for involvement of children based on the determinations specified in that category. The documentation may be in the IRB/EC approval letter or in other official correspondence from the IRB/EC to the investigator.

This documentation will be required to complete MTN protocol registration for all clinical studies enrolling children or adolescents that are reviewed by an IRB/EC. This requirement applies to the initial and annual IRB/EC reviews of research protocols and to any subsequent reviews of amendments or Letters of Amendment involving potential study risks or benefits. Protocol registration will not be approved if this documentation is not received.

Below are allowable risk/benefit categories for involving children and adolescents as subjects:

45 CFR §46.404 Risk not involving greater than minimal risk.

45 CFR §46.405 Research involving greater than minimal risk but presenting the prospects of direct benefit to the individual subjects.

45 CFR §46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition.

45 CFR §46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (This category requires a special level of Department of Health and Human Services beyond that provided by the IRB/EC review. For further information, see http://www.hhs.gov/ohrp/children/guidance_407process.html May 26, 2005 guidance, "Children involved as subjects in research: Guidance on the HHS 45 CFR 49.407 review process."

6.7 Registration Process for MTN 004 Sites

Each site that intends to implement MTN 004 new or revised protocol must receive BOTH the approval of the IRB responsible for that site AND the approval of PAMAB/NICHD (through the ATN-DOC) before enrolling subjects in that study. In order to receive approval from the ATN-DOC for each version of the protocol, a site must ship overnight or fax all required documentation to the Regulatory Department of the ATN-DOC at the address listed at the end of Section 6.9. After these materials are submitted, the regulatory associate will follow up with the site if necessary to retrieve any missing information. Once these materials are complete and accurate, the ATN-DOC will notify the sites of approval to begin enrolling subjects within three business days.

6.7.1 New Protocol Versions

Once a new version of a protocol is distributed, sites may no longer register for a previous version of the protocol. Sites registered to participate in a previous version of the protocol are required to submit the current amended version to their IRB within 30 calendar days of distribution of the protocol to the sites. Subjects may be enrolled in the previous version for up to 90 days after the new version is distributed to the sites. Once the new

Section Appendix 3-7
The Protocol Registration Policy

version is registered by the ATN-DOC for a site, all active subjects consented under the previous version must be re-consented under the new version. In general, and unless instructed otherwise, subjects will be re-consented at the next research visit after the protocol has been registered by the ATN-DOC.

6.8 Procedures for Protocol Registration

6.8.1 Required Documents

These documents are required for **each protocol and any subsequent version**. The MTN 004 site must keep the original set of protocol registration documents on file. The site must submit for itself and each administratively-distinct subsite **one copy** to the ATN-DOC of the following materials:

- MTN Protocol Registration Checklist (Exhibit __);
- Documentation of IRB approval (see section 6.8.2);
- IRB approved consent forms (see Section 6.3);
- Human Subjects Protection Monitoring Form (Exhibit __).
- A copy of Form FDA 1572
- Completed Clinical Investigator Financial Disclosure Form for each person on Form FDA 1572
- Institute Federal Wide Assurance Number (FWA)
- CV-signed and dated for site IoR
- HSP training certificates for all personnel listed on Form FDA 1572
-

6.8.2 Documentation of IRB Approval

IRB approval must include the following items:

- Complete protocol title;
- Protocol/study number and version number;
- Date of IRB approval;
- Signature of IRB Chairperson or member designee;
- Title of the person signing for the IRB;
- Expiration Date; and
- Documentation of the IRB/EC designation of a risk/benefit category from 45 CFR 46.404-407.

Section Appendix 3-7
The Protocol Registration Policy

6.9 Exemptions

If a site cannot meet all the specific protocol registration requirements as outlined in Section 6.8 (due to IRB constraints, usual practice, or other restrictions), then a request for exemption, with relevant documentation, can be submitted to NICHD Program Staff through the ATN-DOC. These requests will be considered on a case by case basis. An example may include accepting an IRB's internal version numbering system on official IRB correspondence.

Send all registration materials to:

DOC Regulatory Associate: Aileen Kim
Westat
1441 West Montgomery Ave
Room WB 331
Rockville, MD 20850
Phone: 301-738-3642
Fax: 301-692-2149
Email: AileenKim@Westat.com or Regulatory@westat.com
Or

DOC Regulatory Manager: Marci Aderiye
Westat
1441 West Montgomery Avenue
Room WB 346
Rockville, MD 20850
Phone: 240-453-2645
Fax: 301-692-2149
Email: MarciAderiye@Westat.com or Regulatory@Westat.com

Section Appendix 3-7
The Protocol Registration Policy

MTN Protocol Registration Checklist

SECTION I

Date of Submission: |_|_|-|_|-|_|_|_|_|_| Number of Pages **(Including cover)**: |_|_|_|

This registration is for [Site Name]: _____

ATN Site Number: _____

Protocol Number: |_|_|_| Version Number: |_|_|_| Version Date: |_|_|-|_|-|_|_|_|_|_|

Investigator of Record **(Please print)**: _____

Phone Number: _____ E-mail Address: _____@_____

Name of Person Submitting Registration: _____

Phone Number: _____ E-mail Address: _____@_____

Name of Study Coordinator(s) who has/have completed protocol training:
(Please print) _____

Phone Number: _____ E-mail Address: _____@_____

Site Pharmacist **(Please print)**: _____

Fax Number: _____ E-mail Address: _____@_____

Signature of Person Submitting Registration: _____

SECTION II <i>(Check the Type of Submission)</i>	SECTION III <i>(Required Documents)</i>	EMAIL RESPONSE FROM ATN-DOC
<input type="checkbox"/> Protocol Registration	MTN Protocol Registration Checklist plus materials in 6.8.1	Approval of Protocol Registration or Disapproval with request for changes.
<input type="checkbox"/> Corrected materials	As required by ATN-DOC	Approval if changes are complete and accurate.
<input type="checkbox"/> Annual IRB Renewal	MTN Protocol Registration Checklist, IRB Approval Letter, plus consent forms (if applicable)	Approval of IRB Renewal or Disapproval with request for changes.
<input type="checkbox"/> Deregistration/Study Closure	MTN Protocol Registration Checklist Documentation of IRB approval	ATN-DOC acknowledges closure (NO APPROVAL NEEDED)
<input type="checkbox"/> Other – Please explain _____	MTN Protocol Registration Checklist Documentation of IRB approval	Acknowledgment of receipt for all but Early Termination. (NO APPROVAL NEEDED UNLESS EARLY TERMINATION)

Human Subjects Protections Monitoring Form

Site Number: | | | | | Protocol/Study Number: | | | | | Version Number: | | | | |

Signature of Person Completing this Form: _____ Date: | | | | |

Please review the Protocol's Human Subjects Section and complete this form.

Check here if this study requested no exemptions or waivers. (STOP)

1. Did this study request an exemption as not constituting human subjects research? Yes No (Go to Q2)

1a. Did you request this exemption from your IRB? Yes (Go to Q1b) No
If no, explain why not

1b. Did your IRB grant the exemption? Yes (STOP) No
If no, explain why not

2. Did this study request a waiver of written informed consent? Yes No (Go to Q3)

2a. Did you request this waiver from your IRB? Yes (Go to Q2b) No
If no, explain why not

2b. Did your IRB grant the waiver? Yes (Go to Q3) No
If no, explain why not

3. Did this study request a waiver of parental permission for all youth age 12 and older? Yes No (Go to Q4)

3a. Did you request this waiver from your IRB? Yes (Go to Q4) No
If no, explain why not

3b. Did your IRB grant the waiver? Yes (Go to Q4) No
If no, explain why not

4. Did this study request a waiver of parental permission conditional on specific criteria (e.g., 16 yrs or older, accessing care alone, and/or other criteria)? Yes No (STOP)

4a. Did you request this waiver from your IRB? Yes (STOP) No
If no, explain why not

4b. Did your IRB grant the waiver? Yes (STOP) No
If no, explain why not

Section 4. Participant Accrual

This section provides information on requirements and procedures for recruiting, screening, and randomizing/enrolling participants onto MTN 004.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

For Version 3.0 of the protocol, the accrual targets will be 61 women across all sites (this includes the seven women previously enrolled in Version 2.0 of the protocol). For each site, accrual will begin after all applicable approvals are obtained and a site-specific study activation notice issued. The accrual of an additional 54 eligible participants (for a total of 61 participants) with normal reproductive tracts is expected to require the screening of approximately 160 volunteers. The target for retention will be 95% of enrolled participants over the 21-day follow-up period. For purposes of assessing the primary safety endpoint among women with at least 80% adherence to study product, participants with less than 80% adherence (per participant self-report and excluding site-initiated product holds) will be replaced. (Adherence, per protocol, is defined as application of at least 80% of the expected number of doses of study product over the two weeks of product use). Therefore, it is anticipated that approximately 64 women will be enrolled in the study (57 women under Version 3.0, and seven women under Version 2.0). Accrual is anticipated to take approximately 14 months.

Once accrual is initiated at each site, study staff will report the number of participants screened for and enrolled in the study to the MTN CORE on a weekly basis. To facilitate weekly reporting, sites are encouraged to develop a participant tracking database. Based on information received from each site, the CORE will distribute a consolidated cross-site accrual report to the Protocol Team. The SDMC will report to the Protocol Team the number of participants enrolled based on data received and entered into the study database (Refer to Section 16 for more information about SDMC reporting).

Note: Any participant tracking database that is developed by a site is to be used for tracking purposes only. It must not be used to record source data or to generate source documents. All information entered into the database must be based on other source documents contained in participants' study charts.

Approximately every four weeks during the accrual period, the Protocol Team will review performance and data from each site to determine whether accrual targets must be adjusted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual at each site. Findings and recommendations from these reviews will be communicated to each study site, and the sites will adjust their accrual efforts accordingly. The Protocol Team will make every effort to complete accrual approximately 14 months from study initiation.

Throughout the accrual period, and additionally as accrual comes to an end at each site, care must be taken to manage the recruitment, screening, and enrollment process in order not to exceed site-specific accrual targets. This is important in the last 4-8 weeks of accrual at each site, since during this time enrollment must be monitored closely, and potential participants must be informed that although they may screen for the study, they may not be enrolled if the target sample size is reached before they are able to complete the screening and enrollment process. This may be difficult to explain to potential participants, especially those who are very interested in taking part in the study. Therefore both sites are advised to work with their community advisory board/group members to develop strategies to address this issue several weeks to months before the end of accrual at the site.

Site staff is responsible for establishing a standard operating procedure (SOP) for participant accrual and for updating the SOP and recruitment efforts undertaken if needed to meet site specific accrual goals. The accrual SOP minimally must contain the following elements:

- Site-specific accrual goals
- Methods for tracking actual accrual versus accrual goals
- Recruitment methods and venues
- Methods for identifying the recruitment source of participant who present to the site for screening
- Methods for timely evaluation of the utility of recruitment methods and venues
- Pre-screening procedures (if any)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

4.2 Screening and Enrollment

The study screening and enrollment procedures are described in detail in the protocol and visit checklists contained in Sections 2 and 7 of this manual, respectively. Informed consent procedures are described in Section 5 and instructions for performing clinical and laboratory screening procedures are included in SSP Sections 10 and 12, respectively. Several possible screening and enrollment scenarios are presented for illustrative purposes in Section Appendix 4-1.

4.2.1 Definition of Screening

The term “screening” refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN 004. The study eligibility criteria are listed in protocol Section 5. Figure 4-2 provides further information on the timing of assessment for each eligibility criterion. Required screening procedures are listed in protocol Section 7.

It is the responsibility of the site Investigator of Record and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study. Each study site must establish an SOP that describes how study staff will fulfill this responsibility. This SOP minimally must contain the following elements:

- Eligibility determination procedures, including:
 - During-visit eligibility assessment procedures
 - Post-visit eligibility assessment and confirmation procedures

- Final confirmation and sign-off procedures prior to enrollment
- Documentation
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

Should site staff discover that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee must contact the MTN 004 Protocol Safety Review Team (PSRT) for guidance on subsequent action to be taken. PSRT contact details are provided in Section 11 (Adverse Event Reporting and Safety Monitoring) of this manual. Site staff must also complete a protocol deviations form in accordance with the guidelines of the MTN Manual of Operations.

**Table 4-2
Timing of Eligibility Assessments for MTN 004**

	Assessed At Screening Visit 1	Assessed At Screening Visit 2 /Enrollment
Inclusion and Exclusion Criteria		
Between the ages of 18 and 24, inclusive, at the time of screening and enrollment as verified by site SOP. In PR, 18-20 years eligible if legally emancipated, w/IRB waiver, or parental consent	X	
Be willing and able to provide written informed consent	X	X
Be in general good health	X	X
Be HIV uninfected	X	X
Have a normal Pap Test, or be able to document a normal Pap Test (in the 12 calendar months prior to screening)	X	
Predictable menstrual cycle, w ≥ 21 days between menses (does not apply to pts using hormonal contraception)	X	
Be sexually active, defined as having had penile-vaginal intercourse at a minimum average of at least once per week in the 30 days prior to screening	X	
Be willing to use an effective method of contraception during the study, defined as either a hormonal based method (except vaginal rings); an IUD (inserted at least 30 days prior to enrollment); female sterilization, or sexual activity with a documented vasectomized partner(s). <i>Note: Self-report is acceptable documentation for vasectomized partners.</i>	X	X
Willing to abstain from oral-vaginal and penile-anal intercourse for duration of study participation	X	
Visualization of vaginal and cervical anatomy that lends to colposcopy	X	X
Be willing to undergo all study related assessments (clinical and laboratory), including speculum examination, colposcopy, urine testing and blood draws, and, adhere to follow up schedule as required by the protocol	X	X
Willing to abstain from use of other intravaginal products and/or devices, including sex toys, from 72 hours prior to enrollment through 3-week/Early Termination visit	X	
Agree to not participate in other drug or device study during study participation	X	

Willing to use 3% w/w SPL7013 Gel VivaGel [®] , VivaGel [®] placebo or HEC placebo as required	X	
Urine negative for pregnancy at screening and enrollment	X	X
Agree to have partner use study provided condoms for each act of intercourse during study participation	X	
Has not participated in any other device or drug study in the 30 days prior to enrollment	X	X
No history of adverse reaction to latex or any other component of study products	X	
No reported history of male sex partner having an allergic reaction to latex	X	
Using at enrollment, or intention to use diaphragm, vaginal ring, and/or spermicide for contraception during study participation	X	X
Not pregnant or breastfeeding at screening or enrollment, or has had any form of pregnancy within 90 days of enrollment	X	X
No grade 3 or higher laboratory abnormality, as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Experiences, based on hematology, liver function, creatinine, and coagulation testing performed by study staff at screening and confirmed by retest and/or redraw	X	X
No gynecologic surgical procedure in 90 days prior to enrollment (e.g., biopsy, tubal ligation, dilation and curettage, etc.)	X	X
No abnormal finding on physical or pelvic examination which precludes participation in the trial	X	X
No STI or RTI at screening or enrollment requiring treatment. (See protocol Section 5.3 for details)	X	X
In 6 months prior to enrollment, not diagnosed with or treated for any STI (except genital HSV recurrence or pelvic inflammatory disease)	X	X
No use of oral and/or vaginal preparations of antibiotic or antifungal medications at screening or within 30 days prior to enrollment	X	X
No injection of non-therapeutic drugs in the 12 calendar months prior to enrollment	X	X

This schedule presents minimum requirements for ascertainment of each eligibility criterion. Additional assessments related to any criterion may be performed if clinically indicated. Assessments required at Screening may be conducted over multiple visits/days. All Enrollment assessments must be conducted within 36 days of providing informed consent for screening, and with the exception of Informed Consent for Enrollment and Specimen Storage, must be completed at a single study visit. Informed Consent for Enrollment and Specimen Storage may be discussed and obtained prior to the Enrollment Visit as needed.

Although participants will be asked about pregnancy history, history of gynecological procedures, and history of non-therapeutic injection drug use at Screening, the time frame for these criteria is relative to the day of enrollment. Similarly, although participants will be asked about participation in any other spermicide and/or vaginal microbicide study or any device or drug study at Screening, the 30-day time frame for this criterion is relative to the day of Enrollment.

4.2.2 Definition of Enrollment

Participants will be considered enrolled in MTN 004 once the assigned MTN 004 Clinic Randomization Envelope (or MTN 004 Replacement Envelope, for replacement participants) has been opened. Further information on methods and materials for random assignment is provided in Section 4.2.7.

4.2.3 Screening and Enrollment Timeframe

All protocol-specified screening procedures must take place within -36-days of enrollment (Day 0), beginning on the day the potential participant provides written informed consent for screening. For example:

- A potential participant who signs her screening informed consent form on September 4, 2008 could be enrolled on any day up to and including October 10, 2008.

September 2008						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	2	3	4 Screening Consent	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

October 2008						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	4
5	6	7	8	9	10 Last day to Enroll	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

To help ensure that the 36-day screening period is not exceeded, study staff are strongly encouraged to highlight the allowable screening period on their screening and enrollment visit checklists (as shown in Section 7 of this manual).

If all screening and enrollment procedures are not completed within 36 days of obtaining informed consent for screening, the participant must repeat the entire screening process, including the screening informed consent process, but not including PTID assignment, which is not repeated. The term “screening attempt” is used to describe each time a participant screens for the study.

4.2.4 Screening and Enrollment Logs

The DAIDS Policy: *Requirements for Essential Documents in DAIDS Funded and/or Sponsored Clinical Trials* requires study sites to document screening and enrollment activity on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one log. Figure 4-3 presents a sample screening and enrollment log suitable for use in MTN 004. Study sites are encouraged to reference the item numbers on the Screening Summary non-DataFax form (see Section 14) when recording the reason for screening failure/discontinuation on the screening and enrollment logs.

Figure 4-3

Sample MTN 004 Screening and Enrollment Log							
Site Name, Clinic Name, and Location:							
	Participant ID	Date Screened/ Consent Signed*	Eligible?		Enrollment/ Randomization Date	If not enrolled, specify reason (include all applicable codes).	Staff Initials
1			Y	N			
2			Y	N			
3			Y	N			
4			Y	N			
5			Y	N			
6			Y	N			
7			Y	N			
8			Y	N			
9			Y	N			
10			Y	N			
11			Y	N			
12			Y	N			

* Note: Women should not be considered screened unless they have completed the screening informed consent process.

4.2.5 Assignment of Participant ID Numbers

SDMC will provide each study site with a listing of Participant ID (PTID) numbers for use in MTN 004. As shown in Figure 4-4, the listing will be formatted such that it may be used as the log linking PTIDs and participant names at each site.

Further information regarding the structure of PTIDs for MTN 004 can be found in Section 14. PTIDs will be assigned to all potential participants who come to the clinic for a screening visit. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts she undergoes. Site staff is responsible for establishing SOPs, proper storage, handling, and maintenance of the PTID list. Participant confidentiality must be maintained so individual PTIDs are assigned to only one participant, and individual participants are assigned to only one PTID.

Figure 4-4
Sample Site-Specific PTID List for MTN 004

	Participant ID	Participant Name	Date	Staff Initials
1	XXX-00001-Z			
2	XXX-00002-Z			
3	XXX-00003-Z			
4	XXX-00004-Z			
5	XXX-00005-Z			
6	XXX-00006-Z			
7	XXX-00007-Z			
8	XXX-00008-Z			
9	XXX-00009-Z			
10	XXX-00010-Z			

4.2.6 Screening HIV Testing

HIV infection status at screening will be assessed using an FDA-approved enzyme immunoassay (EIA), illustrated in Appendix III of the protocol. If the EIA is non-reactive, the participant will be considered HIV-uninfected. If the EIA is reactive, an FDA-approved Western Blot (WB) test will be performed. If the WB is negative, the participant will be considered HIV-uninfected. If the WB is positive, the participant will be considered HIV-infected and should not be enrolled in the study. Although not enrolled in the study, the participant should return to the clinic for a second, confirmatory specimen. If the WB is indeterminate, the participant will be asked to return to the study site in approximately one month for re-testing. This participant also should not be enrolled in the study.

Further instructions for performing HIV tests during screening are provided in Section 12. At each site, all tests must be documented on local laboratory log sheets or other laboratory source documents. Also at each site, a second independent clinic or laboratory staff member trained in proper HIV testing and result recording procedures must review, verify, and sign-off on test results prior to disclosure of results to participants. (Refer to SSP Section 12 on Laboratory Considerations).

4.2.7 Random Assignment Overview

At each study site, enrolled participants will be randomly assigned in equal numbers to the three study treatment arms. The study arms will be double-blinded to Study Gel, meaning that both site staff (clinic, pharmacy, and lab) and participants will not be provided information on the identity of the specific gels to which participants have been assigned.

Note: For each participant, random assignment will take place **after** the participant has been confirmed as eligible and willing to take part in the study, as documented by her signing or marking the enrollment informed consent form. The in-clinic randomization procedures and a possible randomization and first gel dispensation scenario are presented for illustrative purposes in Section Appendix 4-2.

The SDMC will generate and maintain the study randomization scheme and associated materials, which consist of the following:

- MTN 004 Clinic Randomization Envelopes
- MTN 004 Clinic Randomization Envelope Tracking Records
- MTN 004 Prescriptions
- MTN 004 Replacement Envelopes
- MTN 004 Replacement Envelope Tracking Records
- MTN 004 Replacement Prescriptions
- MTN 004 Participant – specific Pharmacy Dispensing Records

MTN 004 Clinic Randomization Envelopes will be shipped from the SDMC to each study site. They will be stored in the clinic and assigned in sequential order to participants who have been confirmed as eligible and willing to take part in the study. Envelopes must be assigned in sequential order, and only one envelope may be assigned to each participant. Once an MTN 004 Clinic Randomization Envelope is assigned to a participant, it may not be re-assigned to any other participant. MTN 004 Replacement Envelopes will also be shipped from the SDMC to each study site. They will be a different color than the MTN 004 Clinic Randomization Envelopes and will be stored in the clinic. Site clinic staff will assign the MTN 004 Replacement Envelopes in sequential order to currently enrolled participants who require replacement cartons, and to any participants (confirmed as eligible and willing to take part in the study) who are enrolling to replace a currently enrolled participant with < 80% adherence to study gel. All envelopes are sealed with blue security tape that, when opened, reveals the word “OPENED” in the residue of the tape.

MTN 004 Clinic Randomization Envelope assignment to eligible participants will be documented on the MTN 004 Clinic Randomization Envelope Tracking Record (see Figure 4-5a) that will accompany the randomization envelope shipment to each site. MTN 004 Replacement Envelope assignments to eligible participants will be documented on the MTN 004 Replacement Envelope Tracking Record (see Figure 4-7a). The act of assigning an MTN 004 Clinic Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once an MTN 004 Clinic Randomization Envelope is assigned, the participant is considered enrolled in the study. For replacement participants, the act of assigning an MTN 004 Replacement Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once an MTN 004 Replacement Envelope is assigned to a replacement participant, the participant is considered enrolled in the study.

Each MTN 004 Clinic Randomization Envelope will contain an MTN 004 prescription (see Figure 4-5b), and each MTN 004 Replacement Envelope will contain an MTN 004 Replacement Prescription (see Figure 4-7b). MTN 004 Prescriptions and Replacement Prescriptions will be produced as a two-part no carbon required (NCR) form pre-printed with the site name, site number, clinic name, MTN 004 Clinic Randomization or Replacement Envelope number, and randomization code(s) indicating assignment to either VivaGel[®], VivaGel[®] placebo, or HEC placebo gel. After recording the PTID and signature on the prescription, clinic staff will separate the two parts of the Prescription form and deliver or fax the white original copy to the pharmacy. The original prescription must be delivered to the pharmacist in order for the study product to be dispensed. The MTN 004 Clinic Randomization Envelope or MTN 004 Replacement Envelope and the yellow copy of the associated prescription will be retained in the participant's study notebook. Each site will develop an SOP for writing study prescriptions and dispensing study gel to participants.

MTN 004 Participant-specific Pharmacy Dispensing Records will be shipped from the SDMC to each study pharmacy, and will be used by pharmacy staff to document dispensation of study gel cartons to the participant. These records will be pre-printed with the site name, clinic name, MTN 004 Clinic Randomization Envelope number, first randomization code and second randomization code (indicating assignment to either VivaGel[®], VivaGel[®] placebo, or HEC placebo gel), and will contain a space to adhere the tear-off labels of dispensed cartons of study gel. Site pharmacy staff only will have access to the Participant-specific Pharmacy Dispensing Records. The SMDC will also provide site pharmacy staff with blank MTN 004 Participant-specific Pharmacy Dispensing Records, meaning the records will not contain any pre-printed information. These blank MTN 004 Participant-specific Pharmacy Dispensing Records will be used for replacement participants only.

Site pharmacy staff only will have access to the Participant-specific Pharmacy Dispensing Records. Pharmacy staff will store all study-related pharmacy records and study product securely in the study pharmacy.

4.2.7.1 Replacing Participants

At the Two-Week Clinic Visit, site clinic staff will complete an MTN 004 Participant Replacement Assessment Worksheet (Figure 4-6) for each study participant. The worksheet will identify participants who have not applied at least 80% of the expected number of doses of study product over the two weeks of product use. This assessment will exclude doses missed due to a site-initiated product hold or discontinuation. Participants who are identified as having product adherence of less than 80% will be considered for replacement by the Protocol Team. Sites should notify the Protocol Safety Review Team of any participants with less than 80% product use adherence. The Protocol Team will make the final determination of whether a participant should be replaced.

The rationale for “replacing” participants is to allow for a safety analysis among participants with a minimum amount of exposure to study product; specifically, between eighteen and twenty-five women randomized to VivaGel with at least 80% study gel adherence, between eighteen and twenty-five women randomized to VivaGel placebo gel and eighteen women randomized to HEC placebo gel with at least 80% study gel adherence.

***Note:** If a participant reports significant non-adherence to the study gel prior to the Two-Week Clinic Visit, site clinic staff should NOT hold or discontinue study gel use due to the non-adherence. Rather, site clinic staff should provide additional study gel adherence counseling, and strongly encourage the participant to use the study gel as instructed for the remainder of the two weeks of product use.*

Figure 4-5a
Sample MTN 004 Clinic Randomization Envelope Tracking Record

Site Name:	Pre-print
Clinic Name:	Pre-print

Instructions: Complete one row each time a MTN 004 Clinic Randomization Envelope is assigned to an MTN 004 study participant. All entries must be made in blue or black ink. Corrections may be made by drawing a line through incorrect entries, entering correct information, and initialing and dating the correction.

Clinic Randomization Envelope #	Envelope Assigned to Participant ID #	Date Assigned (dd-MMM-yy)	Time Assigned (00:00-23:59)	Clinic Staff Initials
Pre-print				

**Figure 4-5b
Sample MTN 004 Prescription**

MTN 004 PRESCRIPTION

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:	University of South Florida		
Clinic Name:	Student Health Services	Clinic Randomization Envelope #:	Pre-print
First Randomization Code:	Pre-print	Second Randomization Code:	Pre-print

Participant ID: --

Did the participant provide written informed consent for enrollment into MTN 004?..... *yes* *no* Clinic Staff Initials: _____

MTN 004 Study Gel

Sig: Insert one applicatorful vaginally twice a day in the morning and in the evening (approximately every 12 hours). The evening dose should be administered before the longest period of rest (usually night).

Quantity: Two cartons of study gel. Refill one additional carton at the One-Week Clinic Visit, as authorized by designated clinic staff, unless otherwise directed by designated clinic staff.

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: --
dd MMM yy

Clinic Staff Instruction for Initial Dispensing Only: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense 2 cartons of study gel (10 pre-filled applicators per carton) to the participant.

Clinic Staff Initials: _____ Date envelope opened: --
dd MMM yy

Pharmacy

Figure 4-6 MTN 004 Participant Replacement Assessment Worksheet

Statistical Center for HIV/AIDS Research & Prevention (SCHARP)

MTN 004 Participant Replacement Assessment Worksheet

MTN 004 (136)

Page 1 of 1

Participant ID

Site Number							Participant Number	-				Chk

Visit Date

dd			MMM			yy

1. Total number of study gel applicators participant used (per participant self report):.....

		applicators used
--	--	------------------

Note: The number in item 1 may be obtained by adding up the number of used applicators reported in item 1 of each Study Gel Adherence form completed for this participant.

÷

2. Total number of expected study gel doses:.....

		expected doses
--	--	----------------

Note: Calculate the number in item 2 by adding up the number of morning and evening doses the participant is expected to have used during her study participation. This includes her first study gel insertion at the Enrollment Visit through her Two-Week Clinic Visit.

=

3. Divide the number in item 1 by the number in item 2, then multiply by 100:.....

			% study gel adherence
--	--	--	-----------------------

4. Based on the response to item 3, does the participant need to be replaced?

yes	no
<input type="checkbox"/>	<input type="checkbox"/>

Note: If the number in item 3 (Percentage of study gel adherence) is less than 80%, the participant is non-adherent to study gel (per protocol) and will need to be replaced. Randomize the next participant who enrolls in the study by assigning her the MTN 004 Replacement Envelope pre-printed with the same envelope number that is pre-printed on the non-adherent participant's MTN 004 Clinic Randomization Envelope.

Version 1.0, 27-MAR-07

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0	1
Language	

Staff Initials / Date

Figure 4-7a
Sample MTN 004 Replacement Envelope Tracking Record

Site Name:	Pre-print
Clinic Name:	Pre-print

Instructions: Complete one row each time a MTN 004 Replacement Envelope is assigned to an MTN 004 study participant. All entries must be made in blue or black ink. Corrections may be made by drawing a line through incorrect entries, entering correct information, and initialing and dating the correction.

Replacement Envelope #	Envelope Assigned to Participant ID #	Date Assigned (dd-MMM-yy)	Time Assigned (00:00-23:59)	Clinic Staff Initials
Pre-print				

Figure 4-7b
Sample MTN 004 Replacement Prescription

MTN 004 REPLACEMENT PRESCRIPTION

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:	University of Puerto Rico		
Clinic Name:	Gamma Project/ATN	Replacement Envelope #:	Pre-print
First Randomization Code:	Pre-print	Second Randomization Code:	Pre-print

Participant ID: - -

Did the participant provide written informed consent for enrollment into MTN 004?..... *yes* *no* Clinic Staff Initials: _____

Participant is: *currently enrolled and requesting replacement carton(s)*
 enrolling to replace a non-adherent participant

<p>MTN 004 Study Gel</p> <p>Sig: Insert one applicatorful vaginally twice a day in the morning and in the evening (approximately every 12 hours). The evening dose should be administered before the longest period of rest (usually night).</p> <p>Quantity: Sufficient quantity to last until next study visit. Refill as authorized by designated clinic staff for a period of two weeks from enrollment, unless otherwise directed by designated clinic staff.</p> <p>Authorized Prescriber Name (please print): _____</p> <p>Authorized Prescriber Signature: _____</p> <p>Date: <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <i>dd MMM yy</i></p>
--

<p>Clinic Staff Instruction for Initial Replacement Carton/Replacement Participant Dispensing Only: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.</p> <p>Pharmacy: Dispense <input type="checkbox"/> cartons of study gel (10 pre-filled applicators per carton) to the participant.</p> <p>Clinic Staff Initials: _____ Date envelope opened: <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <i>dd MMM yy</i></p>

Pharmacy

Participant-Specific Procedures

For each participant, random assignment will take place **after** the participant has been confirmed as eligible and willing to take part in the study, as documented by her signing or marking the enrollment informed consent form. The in-clinic randomization procedures listed below will be performed.

In Clinic:

- C1. Obtain the next sequential MTN 004 Clinic Randomization Envelope (or MTN 004 Replacement Envelope for replacement participants) and inspect it to verify that the correct envelope has been obtained and there is no evidence that the envelope has previously been opened or otherwise tampered with. Assign the envelope to the participant and document assignment on the MTN 004 Clinic Randomization Envelope Tracking Record (or MTN 004 Replacement Envelope Tracking Record) by recording the PTID, date assigned, time assigned, and authorized clinic staff initials in the row corresponding to the assigned envelope number.
- C2. Open the assigned MTN 004 Clinic Randomization Envelope (or MTN 004 Replacement Envelope for replacement participants); or, allow the participant to open it herself. Remove the prescription and confirm the information pre-printed at the top of the form. In particular, confirm that the envelope number printed on the prescription corresponds to the envelope number on the outside of the envelope. If the envelope does not contain a prescription, or if any information pre-printed on the prescription appears to be incorrect, contact the SDMC Project Manager and site Pharmacist of Record (PoR) immediately. The PoR will inform the MTN CORE Pharmacist. Do not proceed with randomization of this or any other participant until instructed to do so by the SDMC.
- C3. Provide appropriate information, instructions, and counseling to participant.
- C4. Complete the prescription, as follows:
 - In the top section of the prescription, record the PTID and mark whether the participant provided informed consent to take part in the study. The staff member who marks the informed consent check box is responsible for confirming the presence of a properly signed/signed and dated informed consent form for enrollment prior to recording his/her staff initials beside these boxes.
 - For replacement prescriptions only, mark the box labeled “enrolling to replace a non-adherent participant.”
 - Complete the middle section of the prescription, which includes a space for the authorized prescriber’s printed name, the authorized prescriber’s signature, and the date. Only a site study staff member designated in the site’s delegation of duties as an authorized prescriber of study gel may complete this section. This person also must be listed as an investigator (either the Investigator of Record or Sub-investigator) on the current FDA Form 1572. The date recorded in this section of the prescription is the date upon which the authorized prescriber signs the prescription.
 - Complete the bottom section of the prescription, which includes the number of

cartons to dispense, a space for clinic staff initials, and the date the envelope was opened. The bottom section of the prescription may be completed by any clinic staff member authorized in the site's delegation of duties to determine the quantity of gel to be given to study participants. Once randomized participants receive a standard amount of two cartons at the Enrollment Visit. After the Enrollment Visit, clinic staff will use the Gel Re-supply Worksheet to determine the number of cartons participants should receive during follow-up. It is expected that most participants will receive a standard amount of one carton at the One-Week Clinic Visit.

- C5. Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain and place the yellow copy in the participant study notebook. Also retain and place the MTN 004 Clinic Randomization Envelope (or the MTN 004 Replacement Envelope, for replacement participants) in the participant study notebook. MTN 004 Clinic Randomization Envelopes and MTN 004 Replacement Envelopes may be hole-punched after they have been opened and their contents have been removed.
- C6. Deliver the white original prescription to the study pharmacy, as follows:
- OPTION A: Give the original prescription to the participant to deliver to the pharmacy
 - OPTION B: Deliver the original prescription to the pharmacy
 - OPTION C: Fax a copy of the original prescription to the pharmacy for filling purposes only; deliver the original prescription to the pharmacy by the time of gel pick-up

Note: In the event that pharmacy staff identifies possible errors on the original prescription, they will return the original prescription to clinic staff for clarification or correction. If corrections are required, identical corrections must be made on both the white original prescription and the yellow copy. An identical signed and dated note explaining the corrections also must be recorded on both copies. Identical corrections and notes must be recorded on both copies, on the same date, by the same person. Corrections must only be made by study staff authorized to complete original prescriptions.

- C7. Once the site pharmacist of record has dispensed study gel to the participant, a member of clinic staff will obtain from the site pharmacist (as specified in a site SOP) the randomization code of each carton of study gel dispensed to the participant. The randomization code(s) obtained from the site pharmacist, and the number of cartons dispensed to the participant, should be recorded on the participant's Enrollment form.

Section Appendix 4-1
Screening and Enrollment Scenarios for MTN 004

4-1.1 Suppose Miss X begins the study screening process (i.e., signs the screening informed consent) on June 6 2008, and that based on the protocol-specified screening visit procedures she appears to be eligible for the study. When Miss X's screening lab results are received, however, she is found to have chlamydia. What do you do?

- When Miss X returns for Screening 2/Enrollment (for example on July 10), provide results and refer for chlamydia treatment. Miss X is not eligible for enrollment.

Why? Potential participants diagnosed with an STI or RTI during the screening process or within 6 months of enrollment are not eligible for the study.

4-1.2 Suppose Miss X reports at her first screening visit that she gave birth one week prior to the visit, and after she has finished breastfeeding (if applicable), but she appears to otherwise be eligible and interested in taking part in the study. What should you do?

- Discontinue the current screening attempt and schedule Miss X to return at least 90 days later to re-start the screening process.

Why? Potential participants are ineligible for enrollment in the study if, at the time of the Enrollment Visit, they are within 90 days of their last pregnancy outcome. That is, enrollment must take place on or after the 91st day after the pregnancy outcome date. For Miss X, only seven days have elapsed since her last pregnancy outcome. Miss X may be scheduled to return to re-start the screening process once she is no longer within 90 days of her last pregnancy outcome. At that time she will be required to sign another informed consent form for screening.

4-1.3 Suppose Miss X begins the study screening process on June 6 2008, and that she appears to be eligible after Screening. At the Screening 2/Enrollment Visit, which takes place on July 20, Miss X does not report any STI/RTI symptoms, and otherwise appears to be eligible for the study, but she is diagnosed with bacterial vaginosis (BV) based on Amsel's criteria. What do you do?

- Enroll Miss X in the study on July 20.

Why? Asymptomatic BV is not a study exclusion criterion and does not require treatment per CDC guidelines. Miss X is free of STI/RTI symptoms and therefore is eligible for the study on July 20 despite having been diagnosed with BV that day. (See protocol section 5.3).

Note: In some cases clinicians may exercise clinical judgment and provide treatment for asymptomatic BV. In such cases, treatment must be completed in order for the participant to be eligible to enroll in the study.

Section Appendix 4-1
Screening and Enrollment Scenarios for MTN 004

4-1.4	<p>Suppose in Scenario 4-1.3 that, rather than being asymptomatic, Miss X reports abnormal vaginal discharge and is diagnosed with BV based on Amsel's criteria at Screening 2/Enrollment. What do you do?</p> <ul style="list-style-type: none">• Provide referral for treatment for BV per CDC guidelines (ideally single-dose). Miss X is not eligible for enrollment. <p>Why? Symptomatic BV requires treatment per CDC guidelines, and is an exclusion criterion for the study. (see protocol section 5.3)</p>
4-1.8	<p>Suppose Miss X begins the study screening process on June 6 2008, and that she appears to be eligible after Screening 1. At the Screening 2/Enrollment Visit, which takes place on July 20, a finding involving deep epithelial disruption is observed on pelvic exam, but no other STI/RTI signs or symptoms are present. What do you do?</p> <ul style="list-style-type: none">• Refer Miss X for follow-up care. Miss X is not eligible for the study. <p>Why? Deep epithelial disruption is exclusionary for this study.</p>
4-1.8	<p>Suppose Miss X begins the study screening process on June 6 2008, and that she appears to be eligible after Screening 1. At the Screening 2/Enrollment Visit, which takes place on July 20, a finding involving inflammation of the cervix is seen, but no other STI/RTI signs or symptoms are present. What do you do?</p> <ul style="list-style-type: none">• Refer Miss X for follow-up care. Miss X is not eligible for the study. <p>Why? Per protocol Version 3.0, any finding involving inflammation of the vulva, vagina or cervix is exclusionary for this study.</p>
4-1.7	<p>Suppose Miss X begins the screening process on July 18 2008 and appears to be eligible after Screening 1. Between the Screening 1 and Screening 2 Visits her lab test results are received and a Grade 3 liver function test result is reported. At Screening 2, which takes place on August 6, Miss X reports that she rarely drinks alcohol, but two days before the Screening 1 Visit she attended her sister's wedding and had several glasses of wine. What do you do?</p> <ul style="list-style-type: none">• Complete all required Screening 2 Visit procedures on August 6.• If Miss X appears otherwise eligible for the study, additionally draw blood to repeat her liver function tests.• Schedule another visit (no later than 36 days after Screening Informed Consent was obtained) to take place when the liver function test results are expected to be available.• Defer the study (enrollment) informed consent process and all enrollment procedures until the next visit. <p>Why? Grade 3 lab abnormalities are exclusionary for the study. However, tests may be repeated during the screening process and enrollment may proceed if a non-exclusionary result is documented within 36 days of providing informed consent for screening.</p>

Section Appendix 4-1
Screening and Enrollment Scenarios for MTN 004

4-1.8 Suppose Miss X begins the screening process on July 18 2008, and during the screening process it is discovered that Miss X was previously enrolled in the study before the study enrollment pause. What do you do?

Inform Miss X she is not eligible for re-enrollment in the study and discontinue the Screening process.

Why? Participants who were previously enrolled in the study prior to the enrollment pause are not eligible for reenrollment in the study.

Section Appendix 4-2b
Randomization and First Gel Dispensation Scenarios for MTN 004

4-2.1 On the day of enrollment/randomization, pharmacy staff identify an error on a participant's prescription (e.g., the "Date envelope opened" is incorrect). What do you do?

Pharmacy Staff: Return the original prescription to clinic staff and inform them of the error that must be corrected in order for study gel to be dispensed.

Clinic Staff: The prescription — both the white original and the yellow copy — must be corrected by clinic staff authorized to complete original prescriptions. Refer to the participant's study chart as needed to determine the correct entries to be added to the prescription. Retrieve the yellow copy of the prescription from the participant's study notebook and record identical corrections on both the white original and the yellow copy. Write identical signed and dated notes explaining the corrections on both the original and the copy. Identical corrections and notes must be recorded on both copies, on the same date, by the same person. Corrections must only be made by study staff authorized to complete original prescriptions. Deliver the corrected white original prescription to pharmacy staff. Retain the corrected yellow copy in the participant's study binder.

Pharmacy Staff: Receive the corrected prescription, verify that all entries are now correct, and give gel per Pharmacy SOPs. File the corrected prescription in participant-specific pharmacy files.

4-2.2 On the day of enrollment/randomization, the participant takes the bus home after her visit and leaves both cartons on the bus. She is unable to find and obtain the cartons. What do you do?

Clinic Staff: Document contact with the participant and the loss of the cartons in the participant's chart notes. Ask the participant to return to the clinic as soon as possible for two replacement gel cartons. When the participant returns to the site, complete a Study Gel Request Slip to order the first carton. Record on the Study Gel Request Slip the randomization codes pre-printed on the participant's Clinic Randomization Envelope prescription. To order the second carton, assign and open the Replacement Envelope pre-printed with the same envelope number that is on the participant's original Clinic Randomization Envelope. Complete the Replacement Prescription inside the Replacement Envelope and order one carton on the prescription. Fax both the completed Study Gel Request Slip and completed Replacement Prescription to the site pharmacy. Then, deliver the white original Study Gel Request Slip and white original Replacement Prescription to pharmacy staff. Retain the yellow copies of the Study Gel Request Slip and Replacement Prescription in the participant's study binder.

Pharmacy Staff: Receive the original Study Gel Request Slip and Replacement Prescription, verify that all entries are correct, and give gel per Pharmacy SOPs. File the slip and prescription in participant-specific pharmacy files.

Clinic Staff: When the participant returns for her One-week Clinic Visit, complete the Study Gel Re-supply Worksheet to determine the number of cartons to dispense. Then, complete a Study Gel Request Slip to order the number of cartons indicated on the worksheet. Record on the Study Gel Request Slip the first and second randomization codes that are pre-printed on the participant's Replacement Prescription. (DO NOT record the randomization codes from the participant's original Clinic Randomization Envelope prescription).

Section Appendix 4-2b
Randomization and First Gel Dispensation Scenarios for MTN 004

4-2.3 Continuing from scenario 4-2.2, suppose the participant lost only one carton of study gel. What do you do?

Clinic Staff: Document contact with the participant and loss of the carton in the participant's chart notes. Ask the participant to return to the clinic as soon as possible for one replacement gel carton. When the participant returns to the site, complete a Study Gel Request Slip to order the carton, and fax the slip to the site pharmacy. Deliver the white original Study Gel Request Slip to pharmacy staff. Retain the yellow copy in the participant's study binder.

Pharmacy Staff: Receive the original Study Gel Request Slip, verify that all entries are correct, and give gel per Pharmacy SOPs. File the slip in participant-specific pharmacy files.

Clinic Staff: When the participant returns for her One-week Clinic Visit, complete the Study Gel Re-supply Worksheet to determine the number of cartons to dispense. Then, assign and open the Replacement Envelope pre-printed with the same envelope number that is on the participant's original Clinic Randomization Envelope. Complete the Replacement Prescription inside the Replacement Envelope and order the number of cartons indicated on the worksheet.

4-2.4 A few days after her enrollment/randomization visit, a participant calls the site clinic and says that she thinks she lost some applicators. What do you do?

Clinic Staff: Call the participant, and ask her how many unused, unopened study gel applicators she currently has in her possession. If the participant has enough study gel to last until her One-week Clinic Visit, reinforce proper gel storage and study gel use. Confirm the One-week Clinic Visit appointment with the participant, and document the phone call in the chart notes.

If the participant does not have enough study gel to last until her One-week Clinic Visit, ask the participant to return to the clinic as soon as possible for replacement gel supplies. When the participant comes in, complete a Study Gel Re-supply Worksheet to determine the number of study gel cartons to dispense. Complete a Study Gel Request Slip to order one carton. Record on the Study Gel Request Slip the randomization codes pre-printed on the participant's Clinic Randomization Envelope prescription. If the Study Gel Re-supply Worksheet indicates that the participant needs two cartons to last until her One-week Clinic Visit, also assign and open the Replacement Envelope pre-printed with the same envelope number that is on the participant's original Clinic Randomization Envelope. Complete the Replacement Prescription inside the Replacement Envelope and order one carton on the prescription. Fax the Study Gel Request Slip and Replacement Prescription (if needed to order a second carton) to the site pharmacy. Deliver the white original copy of the Study Gel Request Slip (and Replacement Prescription, if applicable) to pharmacy staff. Retain the yellow copy/copies in the participant's study binder.

Pharmacy Staff: Receive the original Study Gel Request Slip (and original Replacement Prescription, if applicable), verify that all entries are correct, and give gel per Pharmacy SOPs. File the slip (and Replacement Prescription, if applicable) in participant-specific pharmacy files.

Clinic Staff: When the participant returns for her One-week Clinic Visit, complete the Study Gel Re-supply Worksheet to determine the number of cartons to dispense.

- If the participant has not received any replacement gel cartons during her study participation, complete a Study Gel Request Slip to order one carton. Record on the Study Gel Request Slip the

Section Appendix 4-2b
Randomization and First Gel Dispensation Scenarios for MTN 004

randomization codes pre-printed on the participant's Clinic Randomization Envelope Prescription. If the worksheet indicates that the participant needs two cartons to last until her Two-week Clinic Visit, also assign and open the Replacement Envelope pre-printed with the same envelope number that is on the participant's original Clinic Randomization Envelope. Complete the Replacement Prescription inside the Replacement Envelope and order one carton on the prescription.

- If the participant received one replacement carton during her study participation, assign and open the Replacement Envelope pre-printed with the same envelope number that is on the participant's original Clinic Randomization Envelope. Complete the Replacement Prescription inside the Replacement Envelope and order the number of cartons indicated on the worksheet.
- If the participant received two replacement cartons during her study participation (and was assigned a Replacement Envelope at a previous visit), order the number of cartons to dispense by completing a Study Gel Request Slip. Record on the Study Gel Request Slip the first and second randomization codes that are pre-printed on the participant's Replacement Prescription. (DO NOT record the randomization codes from the participant's original Clinic Randomization Envelope prescription).

Section 5. Informed Consent

This section provides information on informed consent procedures for MTN 004. MTN 004 involves three types of informed consent:

- Informed consent for screening
- Informed consent for enrollment
- Informed consent for specimen storage and future research testing of specimens

Potential study participants must provide written informed consent for screening in order to undergo protocol-specified procedures for determining eligibility for study participation. Potential participants who are found to be eligible for the study must then provide written informed consent to enroll in the study and undergo protocol-specified “on study” procedures, including randomized assignment, use of study gels, and completion of follow-up visits and procedures. Informed consent for specimen storage and future research testing is optional. Participants may choose not to consent to specimen collection and storage for future research testing and still be enrolled in the study.

This section contains general information and instructions applicable to all three types of informed consent required for MTN 004. In addition, detailed guidance is provided for the standardized approach (study specific SOP) to the enrollment informed consent process that must be followed at both sites.

5.1 Overview of Informed Consent Requirements and Procedures

Informed consent is a process by which an individual voluntarily expresses her willingness to participate in research, after having been informed of all aspects of the research that are relevant to her decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, involving information exchange, comprehension, voluntariness, and documentation. Each aspect of this process is described in greater detail below. Please also refer to Section 4 of the ICH GCP guideline and the informed consent section of the DAIDS Policy DWD-POL-CL-04.00:

Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials for further guidance on the informed consent process and documentation requirements, which can be found at:

<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/ClinicalSite.htm>.

As noted above, for MTN 004, informed consent is first obtained for screening procedures only. Then, for participants found to be eligible, informed consent is obtained for enrollment. For both screening and enrollment, informed consent must be obtained prior to undertaking screening and enrollment procedures, respectively. For enrolled participants, informed consent also must be construed as an ongoing process that continues throughout the study follow-up period.

Enrolled study participants are asked to provide informed consent for long term storage of blood specimens for future research testing. Participants may choose to not have their specimens collected and stored for future research testing and still enroll/remain in the study.

US regulations (45 CFR 46) specify the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the Investigator of Record (IoR), and by delegation all study staff involved in the informed consent process, to deliver all required information to potential study participants.

Based on the technical and regulatory reviews that are completed as part of the MTN protocol development and study activation processes, there is adequate assurance that once Westat or MTN CORE (FHI) has “activated” a site for study implementation, the site-specific informed consent form contains all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It is also the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to potential study participants
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the participant comprehends the information
- Document the process

Per Section 13.4 of the MTN 004 protocol, this study does not plan to enroll illiterate individuals. However, if an illiterate woman is interested in participating, the site must follow the ICH GCP guidelines for consenting an illiterate participant.

As a condition for study activation, each study site must establish an SOP for obtaining informed consent from potential study participants that ensures that all of the above-listed requirements are met. The SOP must be consistent with the DAIDS Policy: *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. It is recommended that the SOP contain the elements listed below and that each site seek IRB/EC review and approval of the SOP.

- The minimum legal age to provide independent informed consent for research at the study site
- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy
- Procedures for providing all information required for informed consent to the participant
- Procedures for ascertaining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Considerations and requirements for illiterate participants,
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures (e.g., color-coding) to ensure that the different study informed consent forms are easily distinguished and used appropriately
- Procedures for implementing a change in the version of the informed consent form used
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

5.2 Informed Consent for Screening

At each study site, the informed consent process for screening will be conducted according to site SOPs. Informed consent for screening must be obtained prior to performing any study screening procedures. For participants who do not consent to screening, no screening procedures should be performed and no data that can be linked to the participant's name or other personal identifier(s) should be recorded.

5.3 Informed Consent for Enrollment

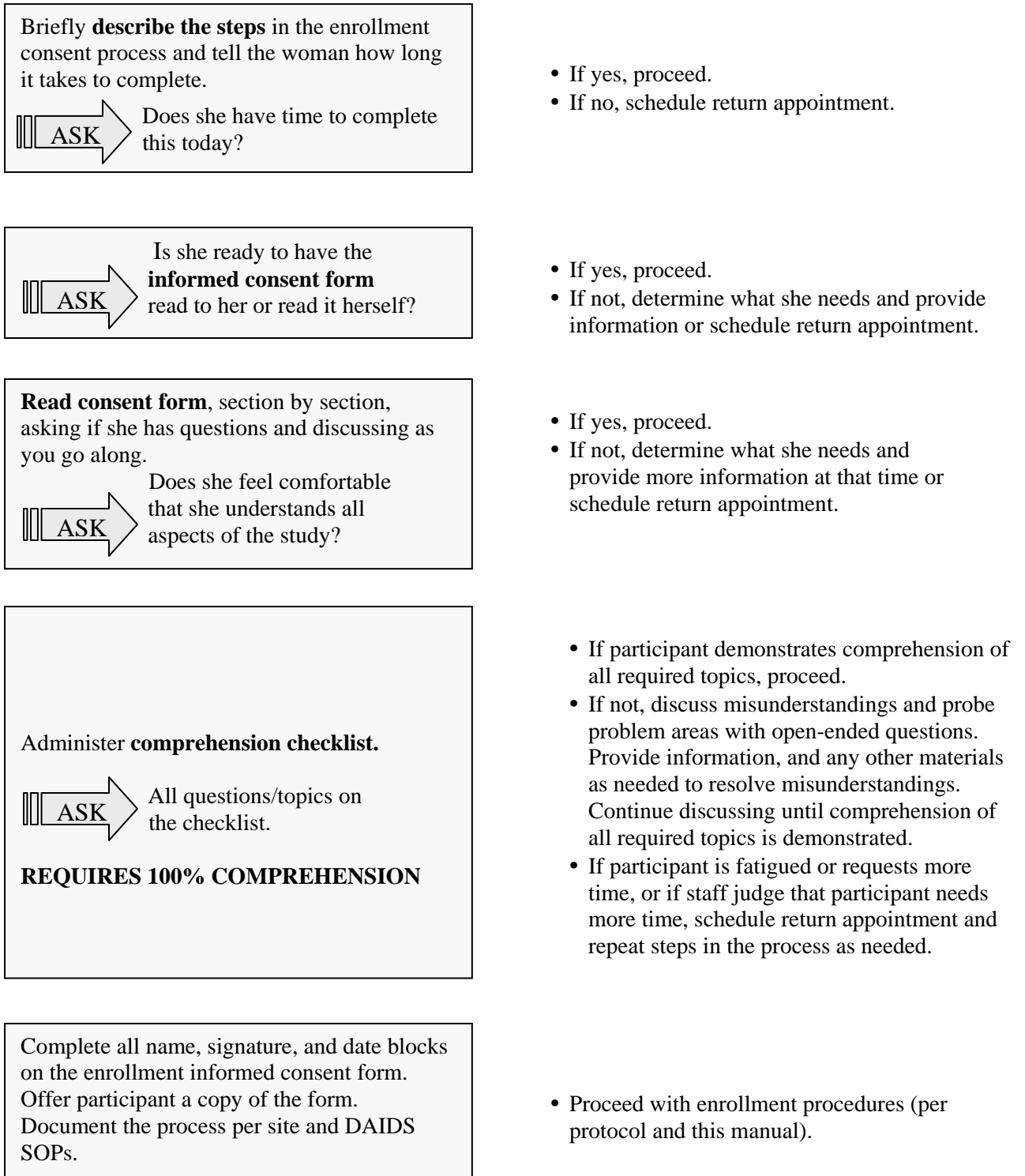
At each study site, the informed consent process for enrollment will be conducted according to site SOPs. However, site specific SOPs must reflect the standardized approach to the enrollment informed consent process that is described in this section. Informed consent for enrollment must be obtained prior to performing any study enrollment or "on-study" procedures. An overview of the standardized approach to the enrollment informed consent process is provided in Figure 5-1. Additional details related to key steps in the process are provided in the remainder of this section.

5.3.1 Informed Consent Support Materials

- **Site-specific informed consent forms:** The informed consent forms used at each site must be reviewed and approved by study site IRBs/ECs prior to their use. After the forms are approved, each site is responsible for preparing bulk supplies of their approved forms and for only using the currently approved versions of the forms at all times during the study.

It is recommended that each site consider the use of color-coding or other techniques to ensure that the study informed consent forms are easily distinguished and used appropriately (such as a yellow cover sheet for screening, blue for enrollment, etc.). At the beginning of the study, bulk supplies of the screening and enrollment informed consent forms should be prepared.

**Figure 5-1
Overview of MTN 004 Enrollment Informed Consent Process**



- **Visual Aids:** Use of visual aids is encouraged throughout the informed consent process to facilitate participant comprehension. Each site should determine the most appropriate visual aids for its study population and ensure that a “kit” containing each of these aids is available in each room where informed consent discussions take place. In addition to the visual aids decided upon at each site, it may be helpful to point out such things as a locked file cabinet, a referral clinic across the way, or a calendar on the wall. It is not necessary to use each visual aid with each participant. Study staff should use their best judgment of each participant’s information needs and how best to address those needs.

Suggested visual aids for each site to consider using are as follows:

- Calendar
- Sample applicator
- Sample product carton
- Urine specimen cup
- Blood collection tubes
- Vaginal and/or pelvic model
- Speculum
- Randomization explanation visual aids (e.g., sack or box containing three items of different colors)
- Placebo explanation visual aids (e.g., hair gels with and without straightener, food flavoring sauces in sweet and non-sweet versions)

If the site personnel choose to use vaginal and pelvic models, remember that participants may not be familiar with such models. Introduce the models in a sensitive manner and use information, rapport, and humor to help make the participant feel comfortable with the models. Be sure that all staff that may use the model are able to explain the anatomical parts of the model as needed.

When using a vaginal model to demonstrate gel use, suggest to the participant that she may wish to expel a small amount of the gel from the applicator to provide lubrication before inserting the applicator. Always hold the applicator in the middle of the barrel and insert it so that half is inserted inside and half is visible on the outside of the vagina. Once the applicator is inserted, push the plunger all the way in to illustrate how the study gel will be administered into the vagina. Remove the applicator and remind the participant that all used applicators should be discarded.

5.3.2 Comprehension Assessment

The staff person conducting the enrollment informed consent process with a potential participant is responsible for determining whether the participant comprehends the information provided to her. The MTN 004 Enrollment Informed Consent Comprehension Checklist (see sample in Section Appendix 5-3) will assist staff in assessing participant comprehension and targeting follow-up educational efforts to ensure that participants understand all information required to make an informed decision about whether to enroll in the study.

The sample checklist will be administered by study staff to each potential participant after she has completed the informed consent discussions described above and before she is asked to sign on the enrollment informed consent form. The checklist should not be presented to participants as a “test,” but rather as a way of double-checking that study staff have fulfilled their responsibility to provide all information needed for the participant to make an informed decision about enrolling in the study.

It is expected that the checklist will be administered by the same staff member who conducted the enrollment informed consent discussion with the participant; this will increase the likelihood of an accurate assessment of the participant’s comprehension. If more than one staff member spent time with the potential participant during the informed consent process, the checklist should be administered by the person who spent the most time with the participant.

The checklist is structured around open-ended questions that correspond with the required elements of informed consent for research. Each question should be read to the potential participant, giving her time to respond to each one.

Each question should be satisfactorily answered by the participant before moving to the next question. For each question, the checklist specifies particular points that must eventually be included in the participant’s response. When the potential participant mentions one of the required points, study staff should check off that point. If the participant does not mention one or more of the required points, study staff should follow-up with another open-ended question to elicit a response about that point. For example, one of the required points in Question 1 is “study is testing an experimental gel.” If the potential participant does not mention this in her initial response to Question 1, the study staff member may then ask “Can you tell me what is being tested in this study?” If the participant responds correctly, the point may then be checked off. All required points must be satisfactorily addressed by the participant, and checked off, before proceeding to the final informed consent decision and signing or marking of the enrollment informed consent form.

When responding to the various questions, potential participants may report back more information than is included on the checklist. This is acceptable, as long as the required information is reported back. If the additional information reported by the participant applies to another question on the checklist, study staff may go ahead and check off that point. If any misinformation is reported back, study staff should explain the correct information before proceeding to another question.

Once administration of the comprehension checklist discussion begins, it is possible that the participant may spontaneously mention many of the required points, without each separate question being asked. In these cases, study staff should check off the relevant points on the checklist and then ask the remaining questions, or probe about the remaining points. It doesn’t hurt to ask a question that a participant may have already answered in her response to a previous question. However, if staff is confident that a previous response was adequate, the specific question and/or point does not need to be repeated.

It is expected that study staff administering the informed consent process and checklist will be sufficiently knowledgeable about MTN 004 to make good judgments about potential participants' grasp of the required information. It is possible that a participant might repeat the correct information, yet the staff member may not be convinced that she really understands it. In these cases the staff should decide if further explanation or discussion is needed before proceeding to the final informed consent discussion and signing the informed consent form. The further explanation or discussion could take place at the same visit or another visit might be suggested/scheduled.

Whenever additional information or explanation is needed, all the informed consent support materials may be used. Study staff should decide which materials may be most helpful to each participant. Some potential participants may be more comfortable interacting with the same study staff person throughout the informed consent process. However, another staff member may be consulted, if necessary or desired, to help explain problematic concepts and/or respond to participant questions or concerns.

The comprehension checklist is considered a study source document that should be completed, handled, and retained in the participant's study chart like any other source document. After administering the checklist, study staff should carefully review the checklist to verify that all required points have been satisfactorily addressed by the participant and that this is adequately documented on the checklist (i.e., with a check mark beside each point). Failure to document participant comprehension of all required points on the checklist will be considered an informed consent and enrollment violation. Comments may be recorded in the designated column on the checklist (and on the back of the checklist if additional space is needed), however this is not required. Lastly, after the enrollment consent process is completed, the final outcome of the process should be recorded in the bottom left corner of the checklist and the staff member who completed the checklist should ensure his/her signature in the space provided.

5.4 Informed Consent for Specimen Storage and Future Research Testing

At each study site, the informed consent process for specimen storage and future research testing will be conducted according to site SOPs among enrolled study participants. For participants who do not consent to specimen storage and future research testing, specimens will not be collected and stored for specimen storage purposes (specifically, plasma archive specimens at the Enrollment and the 2-Week Study Visits). Any leftover specimens collected for study procedures will be destroyed.

5.5 Documenting the Informed Consent Process

US regulations require that informed consent be documented by "the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

To fulfill this requirement, complete all signature and date blocks on the informed consent form in black or blue ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a participant's full surname, and it is strongly recommended that initials not be used in place of a participant's full first name. However, if a participant commonly signs her name using an initial for her first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

The DAIDS Policy Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials

(<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Regulatory>) lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS Policy must be met. In order to also meet some of the suggestions listed in the DAIDS Policy, site staff may use an informed consent "coversheet" similar to the example included in Section Appendix 5-2. Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for Source Documentation for MTN 004 and should use the coversheet consistently to document all informed consent processes with all participants.

In addition to completing the documentation requirements on the informed consent form itself, each informed consent process must be documented in a signed and dated chart note. It is essential that the note (as well as the dates on the informed consent form itself) document that informed consent was obtained prior to the initiation of any study procedures. The note should also document adherence to the requirements of the informed consent section of the *DAIDS Policy Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

Finally, regulations require that participants be offered a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this in a chart note and offer the participant an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full informed consent form.

Section Appendix 5-2
Sample Informed Consent Coversheet for MTN 004

Participant Name (or PTID):	
Name of study staff person completing informed consent process/discussion (and this coversheet):	
Is the participant of legal age to provide independent informed consent for research?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ STOP. Participant is not eligible for MTN 004.
Date of informed consent process/discussion:	
Time of informed consent process/discussion:	
Language of informed consent process/discussion:	
Was the informed consent process/discussion conducted according to site SOPs for MTN 004?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Record and explain departures from site SOPs below.
Can the participant read?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ A literate impartial witness should be present during the entire informed consent process/discussion. Refer to site and DAIDS SOPs for specific instructions. Record name of witness here: Record relationship of witness to participant here:
Version number/date of informed consent form used during informed consent process/discussion:	
Was all information required for the participant to make an informed decision provided in a language that was understandable to the participant?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Were all participant questions answered?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Did the participant comprehend all information required to make an informed decision?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Was the participant given adequate time/opportunity to consider all options before making her informed decision?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Explain below.
Did the participant accept a copy of the informed consent form?	<input type="checkbox"/> NA (participant chose not to provide informed consent) <input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ Offer alternative form of study contact information to participant.
Notes/Comments (continue on back if needed):	
Signature of study staff person completing informed consent process/discussion (and this coversheet):	

Section Appendix 5-3
Sample Enrollment Informed Consent Comprehension Checklist

PTID:

Date:

Open-Ended Question/Statement		Required Points of Comprehension	√	Comments
1	Please describe your understanding of the purpose of the study	Study is testing an experimental gel		
		Testing to learn if the gel is safe		
		Testing to learn if women will like using the gel		
		The gel may not work to prevent HIV or any other sexually transmitted diseases		
		The gel does not prevent pregnancy		
2	What do you understand that you are being asked to do in this study?	Use the gel twice per day		
		Use condoms with each act of vaginal sex		
		Must not douche or insert other things into vagina		
		Have pelvic exams, and other laboratory tests		
		Come for weekly visits for 3 weeks		
3	What do you understand about possible risks that might happen as a result of being in this study?	Gel may irritate skin inside or outside vagina		
		Gel may have other side effects		
		Possibility of loss of privacy		
	What will happen if you do not join the study?	Free to make her own decisions about joining		
		No effect on access to care when decide to join or not		
5	Please tell me about the different groups of women in the study	The groups receive three different gels – VivaGel, VivaGel placebo, HEC placebo		
		No one knows who receives which gel		
6	How will the information about you be protected?	Participant information is kept under lock and key		
		Only people working in the study have access		
7	What are the benefits to you participating in this study?	HIV testing and counseling, referral for care if needed, (must mention at least one)		
8	What should you do if you have any questions about what is happening in the study	Must articulate how to contact study staff		
Outcome: <input type="checkbox"/> Demonstrated comprehension of all required points, decided to enroll in study <input type="checkbox"/> Demonstrated comprehension of all required points, decided NOT to enroll in study <input type="checkbox"/> Demonstrated comprehension of all required points, deferred enrollment decision to another visit <input type="checkbox"/> Did not demonstrate comprehension of all required points (yet), needs more time/discussion, rescheduled for another visit <input type="checkbox"/> Unable to demonstrate comprehension of all required points, consent process discontinued <input type="checkbox"/> Other (specify): _____				Optional Comment Categories: a. Answered correctly on first try b. Could not answer at first, but answered correctly after some probing/discussion c. Answered incorrectly at first, but answered correctly after discussion d. Not able to answer correctly at this time e. Other (describe)
Staff Signature: _____				

Section 6. Participant Follow-up

This section provides information on requirements and procedures for participant follow-up.

6.1 Study Follow-up Plan and Participant Retention Targets

Each enrolled participant will be followed through week three post enrollment. The target accrual is expected to be completed within 14 months. The protocol team will actively monitor and manage the study accrual process to ensure that the enrollment plan occurs.

To minimize bias and ensure accuracy of study results, each study site will target a minimum retention rate of at least 95% for all enrolled study participants. Further information on MTN 004 retention definitions and procedures is provided in Section 8.

6.2 Types of Follow-up Visits

Throughout the study follow-up period, two types of follow-up visits may be conducted:

- **Scheduled visits** are those visits required per protocol. The protocol specifies that follow-up visits occur on a weekly basis. Within the category of scheduled visits, the term “weekly visits” is used to refer to those visits scheduled to take place in follow-up at Weeks 1, 2, 3. All scheduled follow-up visits are pre-assigned a visit code for purposes of data management as described in Section 14.
- **Interim visits** are those visits that take place between scheduled visits. There are a number of reasons why interim visits may take place (see protocol Section 7.6.8). Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 14.

Additional information related to the scheduling and conduct of scheduled and interim visits is provided in the remainder of this section.

6.3 Follow-up Visit Scheduling

6.3.1 Target Visit Dates

Enrolled participants will be scheduled to complete three follow-up visits. For each participant, follow-up visits are targeted to take place on a weekly basis for three weeks from the participant’s enrollment date. Each participant’s enrollment date is defined as the date upon which she is assigned an MTN 004 Clinic Randomization Envelope (or an MTN 004 Replacement Envelope, for replacement participants). For example, for a participant assigned an envelope on 16 September 2008, follow-up visits will be targeted to take place on 23 September, 30 September, and 07 October. The One-Week and Two-Week Clinic Visits have a visit window of one day prior to through one day after the target date. The Three-Week Clinic Visit has a visit window of one day prior to through three days after the target date. If the target date falls on a Friday and is missed, site staff should make every effort to schedule the visit on the following Monday.

6.3.2 Targeted Phone Call

Enrolled participants will complete a phone assessment at targeted Day 2 Post Enrollment. If it is not possible to conduct the phone assessment Day 2 post enrollment, the assessment can be done 2-4 days post enrollment.

6.3.3 Target Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, each follow-up study visit and telephone assessment has a visit window around the target date (i.e., \pm one day before or after the target date for the Day-2 Phone Assessment, One-Week and, Two Week Clinic Visits, and, \pm one day before or three days after the target date for Three-Week Clinic Visit). Figure 6-1 illustrates the target visit windows for follow-up visits.

Figure 6-1
Target Visit Windows for MTN 004

Screening 1 Visit	Screening 2 Visit	Enrollment Visit	Phone Call	1-Week Clinic Visit	2-Week Clinic Visit	3-Week Clinic Visit
DAY -36 or less	Day -36 or less	DAY 0	Day 2-4	DAY 6-8	DAY 13-15	DAY 20-24

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at one-week intervals, and every effort should be made to do so. Extreme deviation from one-week intervals must be avoided. However, in cases where a participant is unable and/or not available to complete a given scheduled study visit within the window, it is highly preferable to conduct the visit as an “early retained visit” (before the visit window opens) or as a “late retained visit” (after the visit window closes), rather than miss the visit entirely. Such visits should be conducted on a date as close as possible to the visit window. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the weekly visit schedule (see Section 16).

6.3.3 Incomplete Visits

All procedures specified by the protocol to be performed at a particular follow-up visit will be completed at a single visit on a single day. In the event that all required procedures cannot be completed on a single day (for example because the participant must leave the study site before all required procedures are performed), the study site staff is to make every effort to complete the remaining procedures as soon as possible. *Note:* all Enrollment Visit procedures, with the exception of informed consent and web-based questionnaire, must be conducted on the same day.

6.3.4 Missed Visits

A regularly scheduled follow-up visit is considered “missed” when a participant does not complete any of the required visit evaluations [either as an “on-time retained” visit (within the visit window), an “early retained visit” (before the visit window opens) or a “late retained visit” (after the visit window has closed)], and the next visit window has opened. For example, a participant completed her One-Week Visit and then did not return to the clinic until the day her Three-Week visit window opened. She did not complete the Two-Week Visit during the Two-Week visit window, and did not complete the visit as an “early retained visit.” The Three-Week visit window has already opened, so she cannot make up the Two-Week Visit as a “late retained visit.” Therefore, the Two-Week Visit is considered “missed.” A Missed Visit case report form will be completed to document the missed visit (see Section 14). Additionally, clinic staff will document the missed visit in the participants’ chart notes and forward a copy of the signed, dated, chart note to the Pharmacy.

It is imperative that site staff conduct any procedures from the missed visit at the participant’s next study visit. For example, if a participant misses her Two-Week Visit, she should complete all Three-Week visit procedures at her Three-Week Visit, as well as any additional procedures missed at the Two-Week Visit (e.g., PK draw (SPL 7013 blood draw)), and completion of the Study Gel Adherence and Acceptability Assessment CRFs).

6.3.5 Follow-up Visit Scheduling Scenarios

Presented in Section Appendix 6-1 are several follow-up visit scenarios that may occur during MTN 004. These scenarios illustrate that the target visit windows impact whether a completed visit will be considered an “on-time retained” visit or an “early or late retained” visit. The examples also illustrate the complexities that may be encountered when scheduling and completing study follow-up visits in a “real world” setting. Given these complexities, all sites are encouraged to use Participant Visit Tracking Sheets similar to the example in Section Appendix 6-2 for each enrolled participant.

6.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Section 7 and protocol Appendix I. Highlighted for reference below are the primary procedural requirements:

- Urine pregnancy testing is done at every contact
- Colposcopy is done at Enrollment and Two-Week Clinic visits, and may be done at all other visits if clinically indicated
- Blood draws are conducted at Screening visit 1, Enrollment, One-Week, and Two-Week visits
- A Phone Call is conducted on Day 2 - 4
- In addition to the screening behavioral assessment, there are 5 different behavioral measures:
 - Baseline Behavioral (web-based) done at Enrollment
 - Adherence Assessment (CRF), done at One-Week and Two-Week Visits
 - Acceptability and Adherence Assessment (web-based) done at Two-Week Visit
 - Acceptability Questionnaire (CRF), done at the Two-Week Visit
 - Study Burden Questionnaire (web-based), done at the Three-Week Visit

- Abdominal exams and pelvic exams (with concomitant medication review) should be performed at all follow-up visits, and, when clinically indicated, at any interim follow-up visits.

In the event that any study procedures do not take place on the date of the visit (for example, if a woman is menstruating at the time of her One-Week Clinic Visit), those procedures should be completed as soon as possible, as part of a “split” visit. If the participant is unable to make up the missed procedures prior to the opening of her next study visit window, site clinic staff should make up the procedures at the next study visit.

6.5 Follow-up Visit Locations

All visits must take place on-site.

6.6 Study Gel Re-Supply During Follow-up

Steps will be taken at follow-up visits to determine whether a participant remains eligible for continued study gel use per protocol specifications. Protocol Section 9.4 and Protocol Appendix II lists conditions under which participants should be discontinued from study gel use, either temporarily or permanently. The site Investigator of Record (IoR) is responsible for ensuring that these protocol specifications are followed for all participants.

Section 9 of this Study-specific Procedures Manual contains detailed information on site clinic staff procedures for the dispensation of study gel, as well as the return of unused study gel supplies.

6.7 Procedures for Participants Who Discontinue Product

Regardless of the participant retention methods undertaken at each study site, participants may voluntarily withdraw from the study for any reason at any time.

Protocol Section 9.4 specifies procedures for participants who discontinue study gel use. Participants who discontinue study gel because of safety concerns or who become pregnant will be encouraged to remain in the study if they are willing, for safety evaluations according to the study follow up schedule, except no study gel will be dispensed. Study pharmacy staff must be informed of the product discontinuation in writing using the Study Gel Request Slip.

6.7.1 Modified Follow-up Procedures for Participants Who Become Pregnant

Participants who test positive for pregnancy after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule until their study exit date, or until such time that the protocol team decides to enroll another participant to replace her in the study. All protocol-specified procedures will continue except for study gel administration. In addition, a post-study contact will be completed to ascertain the participant’s pregnancy outcome. The site IoR will report the pregnancy to the PSRT.

Study pharmacy staff must be informed of the product hold in writing using the Study Gel Request slip. Clinic staff will attach to the Study Gel Request Slip a signed, dated chart note documenting the participant's pregnancy. Study gel supplies previously dispensed to the participant must be retrieved as soon as possible after pregnancy is confirmed, and a Product Hold/Discontinuation case report form must be completed and transmitted to the SDMC.

For all participants who become pregnant, a Pregnancy Report and History (see Appendix 6-5) form must be completed to report the pregnancy. A Pregnancy Outcome form also must be completed to document the outcome of the pregnancy. Certain pregnancy outcomes also must be reported on Adverse Experience Log case report forms (see Section 14) and/or DAIDS Expedited Adverse Event Forms.

6.7.2 Premature Study Discontinuation for an Individual Participant

Under some circumstances it may be appropriate for the investigator to prematurely discontinue a participant from study participation. These are:

- Failure to attend two consecutive clinic visits
- Repeated non-compliance with treatment as prescribed including male condom use
- Request by participant to withdraw
- Request of primary care provider if the study is no longer in the best interest of the participant.

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for MTN 004

<p>6-1.1 Suppose Miss X enrolls in the study on September 18. What are the target and visit window dates for her visits at One, Two and Three Week Clinic Visits?</p> <table style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th style="text-align: center;"><u>Target</u></th> <th style="text-align: center;"><u>Visit Window</u></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">Week 1</td> <td style="text-align: center;">September 25</td> <td style="text-align: center;">September 24-26</td> </tr> <tr> <td style="text-align: center;">Week 2</td> <td style="text-align: center;">October 02</td> <td style="text-align: center;">October 01-03</td> </tr> <tr> <td style="text-align: center;">Week 3</td> <td style="text-align: center;">October 09</td> <td style="text-align: center;">October 08-12</td> </tr> </tbody> </table> <p>Why? Target dates are set every week from the study enrollment date. The target visit window for the One and Two Week Clinic Visits is \pm one day from the target date, and is – one day and + three days from the Week 3 Visit target date.</p>		<u>Target</u>	<u>Visit Window</u>	Week 1	September 25	September 24-26	Week 2	October 02	October 01-03	Week 3	October 09	October 08-12
	<u>Target</u>	<u>Visit Window</u>										
Week 1	September 25	September 24-26										
Week 2	October 02	October 01-03										
Week 3	October 09	October 08-12										
<p>6-1.2 Suppose Miss X has her Week 1 visit on September 28. What are the target and visit window dates for her visits at Two and Three Week Clinic Visits?</p> <ul style="list-style-type: none"> • Same as above in 6.1.1 <p>Why? Target dates always remain linked to the enrollment date. Target dates do not shift when a previous visit does not take place on the target date.</p>												
<p>6-1.3 Suppose Miss X does not have her Two-Week Clinic visit on the target date of October 02, but presents to the study site on October 4. What do you do?</p> <ul style="list-style-type: none"> • Conduct a Two-Week Clinic visit, per protocol, on October 04. <p>Why? Even though Two- Week window has closed, the Three-Week window has not yet opened. Therefore, the Two-Week visit should be conducted and will be considered as “late retained.”</p>												
<p>6-1.4 Suppose Miss X completes her One-Week Clinic visit on time but then does not present to the study site again until October 8. What do you do?</p> <ul style="list-style-type: none"> • On October 8 (the day the Three-Week visit window opens), consider the Two-Week visit missed; complete a Missed Visit form and fax it to SCHARP. • On October 8, conduct a Three-Week visit per protocol. Also perform any additional procedures from the missed Two-Week visit that are not already done as part of the Three-Week visit procedures and data collections. • If the participant reports an AE that requires clinical follow up, schedule a non-study, post-termination clinic visit to follow-up on the AE. Continue to follow-up on the AE until it resolves or stabilizes. <p>Why? The Two-Week visit window closed on October 03, and the Three-Week visit window opened on October 8. Therefore, the Two-Week visit is considered “missed”. Conduct the Three-Week Visit on October 8; it will be considered “retained” since it is within the Three-Week visit window. In addition, since the procedures for the Two-Week Visit are broader than those for the Three-Week Visit – in particular, the colposcopy, PK, adherence assessment (CRF), acceptability assessment (CRF), and the acceptability and adherence assessment (web-based)– these also must be done to at the Three-Week visit to maintain the integrity of the data collection for study endpoint analysis.</p>												

6-1.5 Suppose Miss X completes her One-Week Clinic visit on September 25 and then presents to the study site complaining of genital pain and irritation on September 28. What do you do?

- Conduct an interim visit on September 28, if the participant is able and willing
- On September 28, complete a urine pregnancy test per protocol section 7.6.8
- Schedule participant for colposcopy, if clinician deems necessary
- Complete a Follow-up Genital Symptoms form (optional, at discretion of site clinic staff)
- Complete a pelvic exam and any clinically indicated testing in response to the participant's symptoms and observed exam findings
- Provide or refer to appropriate medical care
- Complete the Interim Visit, Follow-up Pelvic Exam, and AE Log CRFs
- Schedule participant for follow up as clinically indicated (i.e., schedule an interim visit if necessary); otherwise re-evaluate at Two-Week visit
- Remind participant of Two-Week visit date already scheduled

Why? The participant has presented during an interim time interval to report an adverse event. The Two-Week visit window has not opened yet, so Two-Week visit procedures are not conducted at this visit. A pregnancy test is required, as are any other clinically-indicated tests to evaluate the participant's symptoms.

Section Appendix 6-2
Sample Participant Visit Tracking Sheet for MTN 004

Participant ID Number	
Participant Enrollment Date	

***Instructions:** The Participant Enrollment Date is defined as the date upon which an MTN 004 Clinic Randomization Envelope (or an MTN 004 Replacement Envelope, for replacement participants) is assigned to the participant. Once the enrollment/randomization date is determined, enter target visit dates and visit windows below. File this sheet with the participant's study chart and update it with scheduled and actual visit information at each visit.*

Follow-up Timepoint	Target Visit Date	Visit Window	Scheduled Visit Date	Actual Visit Date	Pelvic Exam Performed?	Colposcopy Performed?	Safety Labs Performed?
Day 2 Phone Assessment							
Week 1							
Week 2							
Week 3							

***Note:** This tracking sheet is not a source document. Information on this sheet is based on other source documents contained in the participant study chart.*

Section Appendix 6-3
Sample Pregnancy Management Worksheet for MTN 004

PARTICIPANT ID:			
BACKGROUND INFORMATION			
First day of last menstrual period			
Date of positive pregnancy test			
Estimated full term pregnancy dates			
PREGNANCY MANAGEMENT INFORMATION		Mark ✓ When Done	Initials/Date/Comments
1	Pregnancy Report and History form completed and faxed to SCHARP		
2	Pharmacy informed of pregnancy		
3	Product supplies retrieved from participant and returned to pharmacy		
4	Product Hold/Discontinuation form completed (items 1-3) and faxed to SCHARP		
5	Pregnancy outcome and outcome date ascertained, based on: <input type="checkbox"/> medical records or other written documentation from a licensed non-study health care practitioner <input type="checkbox"/> verbal report from a licensed non-study health care practitioner <input type="checkbox"/> participant self-report <input type="checkbox"/> negative pregnancy test performed by study staff <i>(medical records should be obtained whenever possible)</i>		
6a	Pregnancy Outcome form completed and faxed to SCHARP		
6b	If applicable, AE Log form completed and faxed to SCHARP		
6c	If applicable, EAE Report completed and faxed to DAIDS Safety Office and Starpharma		
6d	If applicable, SAE Report completed and faxed to Starpharma		

Section 7. Visit Checklists

This section contains examples of checklists detailing the protocol-specified procedures that must be completed at MTN 004 study visits.

The checklists also specify the data collection forms that must be completed at each visit. Detailed procedural guidance for performing clinical and laboratory procedures is provided in Sections 10 and 12, respectively. Detailed forms completion instructions are provided in Section 14.

7.1 Use of Checklists

The visit checklists included in this section are designed to guide site staff in proper study procedures as well as to serve as source documentation of procedures performed at study visits. Note, however, that checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to:

- Explain why procedures in addition to those listed on a checklist were performed
- Explain why procedures listed on a checklist were not performed
- Document procedures performed at interim visits
- Document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements)

See Section 3 for detailed information on source documentation requirements. Tips for completing visit checklists in accordance with these requirements are as follows:

- Enter the participant identification number (PTID) and visit date in the top section of each checklist. If information is written on the front and back of the checklist, enter the PTID and visit date on both sides.
- For follow-up visits, enter the visit code in the top section of each checklist (per the instructions in Section 14) and mark whether the visit is a study exit visit.
- Enter your initials only beside the procedures that you perform. Do not enter your initials beside procedures performed by other staff members. If other staff members are not available to initial checklist items themselves, enter, initial, and date a note on the checklist documenting who completed the procedure, e.g., “done by {name}” or “done by lab staff.”
- If all procedures listed on a checklist are performed on the date entered in the top section of the form, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item.
- If a procedure listed on the checklist is not performed, enter “ND” for “not done” or “NA” for “not applicable” beside the item and record the reason why on the checklist (if not self-explanatory); initial and date this entry.

7.2 Sequence of Procedures

The sequence of procedures presented on the visit checklists is a suggested ordering. In consultation with the MTN CORE, site staff may modify the checklists included in this section to maximize the efficiency of site-specific study operations. Sites may alter the sequence of procedures to suit local staffing and logistical requirements, with the following exceptions:

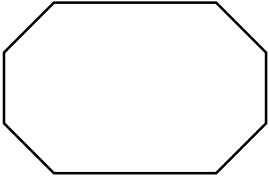
- Informed consent for screening must be obtained before any screening procedures are performed.
- Informed consent for enrollment must be obtained before conduct of any study enrollment or follow-up procedures are performed. Enrollment procedures are listed in the Enrollment sub-sections of protocol Section 7
- Behavioral assessments (web-based surveys, Study Gel Adherence CRF) must be administered prior to adherence counseling.
- Pelvic/colposcopy exam procedures must be performed in the sequence shown on the pelvic exam checklists.

Screening Visit 1: Page 1 of 4

PTID:	Visit Date:
--------------	--------------------

1. _____ Confirm whether the participant is between the ages of 18 and 24 (to provide informed consent for research and meet study age requirement). Explain the two-step (screening and enrollment) informed consent process.
2. _____ Explain study requirements to the participant
3. _____ Review consent with participant according to local SOPs.
4. _____ Obtain written informed consent and complete Consent Process Worksheet.
 - *If the participant does not consent to screening, STOP. Do not fax any forms to SCHARP.*
5. _____ Confirm participant identity. Cross-check with the MTN 004 Name-PTID Link Log to determine whether an MTN 004 Participant ID number has previously been assigned to the participant.
6. _____ Assign an MTN 004 PTID (if not done during a previous screening attempt) by completing a new row in the MTN 004 Name-PTID Link Log.
7. _____ Obtain contact information and record on local form.
 - *If the participant does not provide adequate contact information, and is determined not to be a good candidate for the study (investigator decision) STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the form, but do not fax any forms to SCHARP.*
8. _____ Complete the **Screening Consent** DataFax CRF.

Based on the 36-day screening and enrollment window, beginning on the day informed consent is obtained for screening; enter the participant's last possible enrollment date for this screening attempt

⇒ 
9. _____ Administer the **Demographics** DataFax CRF.
10. _____ Complete the **Screening 1 Visit Eligibility** non-DataFax CRF

Screening Visit 1: Page 2 of 4

PTID:	Visit Date:
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11. _____ Collect approximately 15-60 mL urine and:
Aliquot approximately 5-10 mL and perform qualitative pregnancy test.
Complete testing logs and record result in item 26 of the **Screening 1 Visit Eligibility** form (non-Data Fax CRF).

*If the participant is pregnant, STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the **Screening Summary** form, but do not fax any forms to SCHARP.*

Prepare urine for SDA for gonorrhea and chlamydia at the network lab.
Prepare urine for culture and sensitivity if indicated; refrigerate prior to testing.
Complete dipstick urinalysis; record results for blood, glucose, protein, leukocytes and nitrates according to local SOP. Record results on **STI Laboratory Results** form.
Perform Herpes Culture if indicated

NOTE: If clinically indicated, conduct urine culture and sensitivity, and provide treatment per site SOP. Record results of culture on **STI Laboratory Results** form.

➤ *If the participant's lab results indicate an active STI – with the exception of asymptomatic BV and asymptomatic vulvovaginal candidiasis —she is ineligible for enrollment: STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the form, but do not fax any forms to SCHARP.*

12. _____ Provide HIV pre-test and HIV/STI risk reduction counseling. Obtain informed consent for HIV testing. Provide condoms, other applicable prevention supplies (if any), and referrals if needed/requested.
13. _____ Provide counseling on contraceptive options and male condom use.
14. _____ Do vital signs and record on the **Physical Exam** non-DataFax form.
15. _____ Obtain medical, menstrual, and genitourinary history with documentation of current medications. Record on **Baseline Medical History** form (non-Data Fax), **History of Genital Symptoms** form (non-Data Fax) and **Concomitant Medications Log** Data Fax CRF.
16. _____ Perform abdominal exam and record on **Physical Exam** (non-Data Fax) form.
17. _____ Perform and document pelvic exam using pelvic exam checklist. Complete the **Screening 1 and Enrollment Pelvic Exam** Data Fax CRF.

Screening Visit 1: Page 3 of 4

PTID:	Visit Date:
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18. ____ Determine whether the participant is currently experiencing STI symptoms or has been diagnosed or treated for STI in prior 6 months:
- No
 - Yes ⇒
 - a. ____ Examine the participant if required per site SOP
 - b. ____ Refer to treatment if clinically indicated.

If the participant is currently experiencing STI symptoms or has been diagnosed or treated for an STI in the prior 6 months (with the exception of genital HSV recurrence), she is ineligible for enrollment, STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the form, but do not fax any forms to SCHARP.

19. ____ Complete the **Clinical Eligibility** (non-Data Fax) form.
20. ____ Collect blood and complete an **LDMS Specimen Tracking Sheet** as follows:
- red top tube(s) (no additive)
 - purple top tube(s) (EDTA)
 - blue top tube (sodium citrate)
21. ____ Prepare remaining blood for testing at the local lab:
- Syphilis (RPR) serology
 - CBC (hemoglobin, hematocrit, RBC, WBC with differential, platelets)
 - Coagulation panel (PT INR and PTT)
 - Liver and renal function (AST, ALT, creatinine level) HIV testing
 - HIV Elisa/Western Blot
22. ____ Provide study informational material. Provide site contact information and instructions to contact the site for additional information and/or HIV/STI counseling, if needed, prior to the next visit.
23. ____ Schedule the HIV Results appointment (may also be the Screening 2/Enrollment Visit, based on participant eligibility) taking into account the timing for receipt of the HIV result, receipt of other lab results, the participant's menstrual cycle, and the 36-day screening period.
24. ____ Provide reimbursement for study visit.
25. ____ Complete, Sign and date chart notes for the visit. Review and complete all other participant chart concepts for the visit, but do not fax any forms to SCHARP.

Screening Visit 1: Page 4 of 4

PTID:	Visit Date:
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26. _____ When all lab results are available, transcribe HIV test results onto the **STI Laboratory Results** form. Schedule a visit to inform the participant of her results (this can coincide with the screening 2/Enrollment Visit). Before disclosing results to participant, obtain independent review, verification, and sign-off of the result.

- If the EIA is negative, the participant is considered HIV-uninfected, and eligible for the study. Provide appropriate post-test counseling.*

27. _____ *If the EIA is positive, WB testing is required to clarify the participant's HIV status.*

- Record all WB results on the **HIV Test Results** form.*
- If both the EIA and WB are positive, the participant is considered HIV infected and ineligible for the study (refer to HIV algorithm in Appendix III of the Protocol and Section 12 of the SSP). STOP.*
- If EIA is positive and WB is negative or indeterminate, contact the MTN Network Lab*
- Provide appropriate post-test counseling, and inform the participant that she is ineligible.*
- Refer to local care providers for follow-up and treatment of HIV.*
- Retain documentation completed thus far, and complete the **Screening Summary** form, but do not fax any forms to SCHARP.*

*Note: The **STI Laboratory Results, Safety Laboratory Results, and Pelvic Laboratory Results** forms (and **HIV Test Results** form, when applicable) should be completed when all required test results are available, prior to the Screening 2/Enrollment Visit. Do not fax any forms to SCHARP until the participant is randomized. If the participant is deemed ineligible, retain all of these Datafax forms on site but do not fax any of them to SCHARP.*

Screening Visit 2: Page 1 of 4

PTID:	Visit Date:
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1. _____ Complete participant registration, confirm the participant’s identity, verify her PTID, and determine the current screening attempt number.

2. _____ Review chart notes and other relevant documentation from previous visit(s).

3. _____ Provide and explain all other prior screening test results. Provide post-test counseling for HIV/STIs. Provide male condom counseling.
 - ☞ *If chlamydia, gonorrhea, and/or syphilis infection were identified, and treatment was not provided previously, treatment is required, and participant is ineligible for the study. STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete **Screening Summary** form, but do not fax any forms to SCHARP.*

4. _____ Assess and explain the participant’s current eligibility status. Explain the content and sequence of procedures for the remainder of today’s visit.

5. _____ Update contact information and record on local form

6. _____ Collect ~20 mL urine and:
 - 6a. _____ Aliquot ~5 mL and perform pregnancy test; retain remaining urine for remainder of visit.
 - 6b. _____ Complete testing logs and record result in item 14 of the **Screening 2 Visit/Enrollment Eligibility** form.
 - ☞ *If the participant is pregnant, STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete **Screening Summary** form, but do not fax any forms to SCHARP.*

7. _____ Complete/administer the **Screening 2 Visit/Enrollment Eligibility** form.
 - ☞ *Because it imperative that the potential participant pool is not biased with respect to information on how to answer specific questions, participants – whether deemed eligible or ineligible --should not be given details regarding particular responses and the impact of those response on determining eligibility.*
 - ☞ *If any of the participant’s answers indicate that she is ineligible, finish administering the form through item 13a and then STOP. Inform the participant that she is ineligible. Complete items 14-15 on the form. Retain documentation completed thus far, and complete **Screening Summary** form, but do not fax any forms to SCHARP.*

8. _____ Perform focused medical and menstrual history with documentation of current medications. Record findings on the **Baseline Medical History** form and **Concomitant Medications Log**.

9. _____ If indicated, perform and document pelvic exam on the **Screening 2 Pelvic Exam** form

Screening Visit 2: Page 2 of 4

PTID:	Visit Date:
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10. _____ Determine the participant's current eligibility status based on all screening documentation (refer to the **Screening Summary** form as needed). Explain eligibility status and next steps to the participant.

Currently eligible and enrolling on the same day ⇒ *Continue with the Enrollment checklist.*

Currently eligible but not enrolling on the same day ⇒ *Perform Y5-Y7 on page 3. Schedule Enrollment Visit to occur as soon as possible taking into consideration the 36-day screening period and the participant's menstrual cycle. Refer to last possible enrollment date on page 1 of Screening Visit 1 checklist.*

Not currently eligible ⇒ *Continue as directed in the box below.*

For participants who are not currently eligible: all screening and enrollment procedures must be completed within 36 days of the participant's providing informed consent for screening. Otherwise the entire screening process must be repeated.

Based on all available information, is the participant likely to be confirmed eligible within the 36-day window for the current screening attempt?

Refer to last possible enrollment date on page 1 of the Screening 1 Visit Checklist .

Yes ⇒ *Continue the current screening attempt: perform Y1-Y8 on page 3*

No ⇒ *Discontinue the current screening attempt: perform N1-N8 on page 4.*

Screening Visit 2: Page 3 of 4

PTID:	Visit Date:
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Procedures on this page are for participants who are continuing the current screening attempt, but not enrolling on the same day.

- Y1. ____ If clinically indicated, perform dipstick urinalysis on the aliquot of urine used for pregnancy testing. Complete testing logs and record results in the participant's chart notes only.
- Y1a. ____ If clinically indicated, provide treatment and/or conduct additional UTI work-up per site SOP. Document additional work-up in chart notes only. Document treatment on the **Concomitant Medications Log**.
- Y2. ____ If clinically indicated, transfer remaining (15 mL) urine to conical tube and refrigerate or transfer 2-4 ml directly into a UPT pending delivery to the local lab for shipment to the Network Lab for gonorrhea and chlamydia SDA.
- Y3. ____ If clinically indicated, collect and prepare blood for syphilis serology at the local lab.
- Y4. ____ Schedule next visit to occur when the participant is likely to be eligible, taking into account the participant's current clinical status (including whether STI/RTI treatment and/or a repeat pelvic exam is required), the participant's menstrual cycle, the timing for receipt of lab results if applicable, and the 36-day screening period. Refer to the last possible enrollment date on page 1 of Screening 1 Visit Checklist.
- Y5. ____ Reinforce site contact information and instructions to contact the site for additional information and/or HIV/STI counseling, if needed, prior to the next visit.
- Y6. ____ Reinforce availability of HIV/STI counseling, testing, and STI treatment for partners.
- Y7. Provide reimbursement for study visit.
- Y8. ____ Review and complete signed and dated chart notes for the visit. Review and complete all other participant chart contents for the visit, but do not fax any forms to SCHARP. Do not complete page 4 of this checklist.

Screening Visit 2: Page 4 of 4

PTID:	Visit Date:
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Procedures on this page are for participants who are discontinuing the current screening attempt.

- N1. ____ Provide clinically-indicated follow-up and/or treatment. This may include:
- N1a. ____ Perform dipstick urinalysis on aliquot of urine used for pregnancy test. Complete testing logs and record results in the participant's chart notes only.
 - N1a1. ____ If dipstick clinically indicated, provide treatment and/or conduct additional UTI work-up per site SOP. Document additional work-up in chart notes only. Document treatment on the **Concomitant Medications Log**.
 - N1b. ____ Transfer remaining (15 mL) urine to conical tube and refrigerate or transfer 2-4 ml directly into a UPT pending delivery to the local lab for shipment to the Network Lab for gonorrhea and chlamydia SDA.
 - N1c. ____ Collect and prepare blood for syphilis serology at the local lab.
- N2. ____ Complete the **Screening Summary** form.
- N3. ____ Inform the participant that the 36-day period is likely to be exceeded before she may be eligible for the study. If the participant may be eligible at a future date during the 9-month study accrual period, determine whether she is willing to repeat the screening process:
- No ⇒ *STOP. Retain documentation completed thus far, but do not fax any forms to SCHARP.*
 - Yes ⇒ *Continue with items N4-N8 below.*
- N4. ____ If applicable, schedule another Screening 1 Visit, taking into account the participant's current clinical status, the participant's menstrual cycle, and the timing for receipt of lab results if applicable.
- N5. ____ Reinforce site contact information and instructions to contact the site for additional information and/or HIV/STI counseling, if needed, prior to the next visit.
- N6. ____ Reinforce availability of HIV/STI counseling, testing, and STI treatment for partners.
- N7. ____ Provide reimbursement for study visit.
- N8. ____ Review and complete signed and dated chart notes for the visit. Review and complete all other participant chart contents for the visit, but do not fax any forms to SCHARP.

Screening/Enrollment Pelvic Exam: Page 1 of 3

PTID:	Visit Date:
Please indicate to which visit this checklist applies:	
Screening 1: _____ Screening 2: _____ Enrollment: _____	

1. _____ Using a pencil, write the PTID and specimen collection date on the frosted side of four microscope slides (2 for vaginal wet mount and 2 for vaginal Gram Stain). Then affix a SCHARP-provided PTID label to the other side of each slide (under the pencil markings) and write the specimen collection date in ink on each label.
2. _____ Affix a SCHARP-provided PTID label to a glass or plastic tube containing approximately six drops (100 μ L) of saline. Write the specimen collection date in ink on the label.
3. _____ Explain the exam procedures to the participant and answer any participant questions.
4. _____ Position and drape the participant comfortably.
5. _____ Palpate inguinal lymph nodes. Document abnormal findings on the **Screening 1 and Enrollment Pelvic Exam** form (if this is the Screening 1 pelvic exam), or the **Screening 2 Pelvic Exam** form (if this exam is conducted at the Screening 2 Visit).
6. _____ Inspect external genitalia. Note all findings on the Pelvic Exam Diagrams. Document abnormal findings in items 1-1a on the appropriate pelvic exam form (**Screening 1 and Enrollment Pelvic Exam** form or **Screening 2 Pelvic Exam** form).
7. _____ Insert speculum, using warm water as lubricant if needed. Observe general state of the cervix.
8. _____ Assess for homogenous discharge. Record observation on the **Pelvic Laboratory Results** form.
9. _____ Place pH strip against the lateral vaginal wall until moistened. Alternatively, collect vaginal fluids from the lateral vaginal wall via swab and swab fluids onto the pH strip. Record pH on the **Pelvic Laboratory Results** form.

Screening/Enrollment Pelvic Exam: Page 2 of 3

PTID:	Visit Date:
Please indicate to which visit this checklist applies:	
Screening 1: _____ Screening 2: _____ Enrollment: _____	

10. _____ Swab vaginal fluids from the lateral vaginal wall for Gram stain; do not place the swab in saline, transport medium, or a transport container prior to slide preparation (see also SSP Section 12):
- 10a. _____ Roll the swab across two labeled slides and then allow the specimens to air dry.
- 10b. _____ Document specimen collection on the appropriate pelvic exam form (**Screening 1 and Enrollment Pelvic Exam** form or **Screening 2 Pelvic Exam** form) and on the **LDMS Specimen Tracking Sheet**.
- ☞ If the participant is not enrolled in the study on the same day as this exam, “pending enrollment” should be entered in the Comments section of the LDMS Specimen Tracking Sheet that accompanies the Gram stain slides to the local laboratory.*
11. _____ Swab vaginal fluids from the lateral vaginal wall for wet prep; proceed immediately to Step 12a or place the swab in a labeled glass or plastic tube containing approximately six drops (100 µL) of saline to allow for non-immediate slide preparation and evaluation, as follows (see also SSP Section 12):
- 11a. _____ Smear vaginal fluids from the swab onto two labeled slides.
- 11b. _____ Apply KOH to one slide, perform whiff test, then apply cover slip.
- 11c. _____ Apply saline to the second slide, emulsify, then apply cover slip. Immediately evaluate for trichomonads, yeast buds, pseudohyphae, and clue cells.
- 11d. _____ Evaluate KOH slide for yeast buds and pseudohyphae.
- 11e. _____ If slides are read in-clinic by clinical staff, record results directly onto the **Pelvic Laboratory Results** form. If slides are read by lab staff (either in the local lab or a designated in-clinic lab area) complete testing logs and then transcribe results onto the **Pelvic Laboratory Results** form.
- If lab results are positive for trichomonads, yeast buds, pseudohyphae and/or clue cells, the participant is ineligible, with the exception of asymptomatic BV and asymptomatic vulvovaginal candidiasis. STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, and complete the form, but do not fax any forms to SCHARP.*
12. _____ **Enrollment Visit only:** collect vaginal quantitative culture specimen. Document specimen collection on the appropriate pelvic exam form (**Screening 1 and Enrollment Pelvic Exam** form or **Screening 2 Pelvic Exam** form) and on the **LDMS Specimen Tracking Sheet**.

Screening/Enrollment Pelvic Exam: Page 3 of 3

PTID:	Visit Date:
Please indicate to which visit this checklist applies:	
Screening 1: _____ Screening 2: _____ Enrollment: _____	

13. _____ Inspect cervix and vagina:
13a. _____ Naked eye exam ⇒ Note all findings on the Pelvic Exam Diagrams. Document abnormal findings in items 1-1a on the appropriate pelvic exam form (**Screening 1 and Enrollment Pelvic Exam** form or **Screening 2 Pelvic Exam** form).
14. _____ **Screening 1 only: If applicable, (unless documentation of normal Pap result in 12 calendar months),** collect ecto- and endocervical cells for Pap smear per site SOP.
15. _____ **Enrollment Visit only:** collect cervical swabs for cytokine and innate factors testing. Document specimen collection on the appropriate pelvic exam form (**Screening 1 and Enrollment Pelvic Exam** form or **Screening 2 Pelvic Exam** form) and on the **LDMS Specimen Tracking Sheet**.
16. _____ **Enrollment Visit ONLY:** Colposcopic exam ⇒ Note all findings on the Pelvic Exam Diagrams. Document abnormal findings observed at the Screening 1 Visit in items 2-2a on the **Screening 1 and Enrollment Pelvic Exam** form, and document the degree of cervical ectopy in items 4-4a of the form. Save image(s) of abnormalities electronically (capture of images is optional). Normal images also may be saved.
17. _____ Perform bimanual exam. Document abnormal findings in items 1-1a on the appropriate pelvic exam form (**Screening 1 and Enrollment Pelvic Exam** form or **Screening 2 Pelvic Exam** form).
18. _____ Record the size of speculum used and position of the participant's cervix on the Pelvic Exam Diagrams.

Enrollment: Page 1 of 5

PTID:	Visit Date:
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Will the Enrollment procedures listed below this box be conducted on the same day as Screening Visit 2?

- Yes ⇒ *Continue with the Enrollment procedures on pages 2-4.*
 No ⇒ *Perform procedures B1-B9 in this box and then continue with the Enrollment procedures on pages 2-4 if applicable.*

- B1. ____ Review chart notes and other relevant documentation from previous visit(s).
- B2. ____ Confirm that the 36-day window has not been exceeded for the current screening attempt. Refer to the last possible enrollment date recorded on the Screening Visit 1 checklist.
- B3. ____ Results/Counseling- Provide test results as available. Counseling as needed.
- B4. ____ Update contact information and record on local form
- B5. ____ Review/update the **Baseline Medical History** and **Concomitant Medications Log**. Document review with a signed and dated note on each document reviewed. Initial and date updated entries.
- B6. ____ Collect ~20 mL first void urine and:
B6a. ____ Aliquot ~5 mL and perform pregnancy test.
B6b. ____ Complete testing logs and transcribe result here:

- negative positive

☞ *If the participant is pregnant, STOP. Inform the participant that she is ineligible. Retain documentation completed thus far, record results in the participant's chart notes, and complete the **Screening Summary** form. Do not fax any forms to SCHARP.*

- B7. ____ Review/update the **Screening 2 Visit/Enrollment Eligibility** form. Document review with a signed and dated note on the form. Initial and date updated entries.
- B8. ____ Confirm the participant's current eligibility status based on all screening documentation.
- B9. ____ Explain eligibility status and next steps to the participant.

- Currently eligible ⇒ *Continue with the Enrollment procedures on pages 2-4.*
 Not currently eligible ⇒ *Continue/repeat screening procedures and clinically-indicated treatment and follow-up as needed. Do not complete the remainder of this checklist.*

Enrollment: Page 2 of 5

PTID:	Visit Date:
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1. ____ Confirm that the 36-day window has not been exceeded for the current screening attempt.
2. ____ Results of Screening/Counseling as needed.
3. ____ Explain again the two-step informed consent process and obtain written informed consent for the study. Document the informed consent process in a chart note and on any other documents per site SOP.
 - ☞ *If the participant does not consent to the study, complete the **Screening Summary** form and then **STOP**. Retain documentation completed thus far, but do not fax any forms to **SCHARP**.*
4. ____ Administer informed consent comprehension checklist, according to SOPs
5. ____ Obtain written informed consent for specimen storage and possible future research testing. Document the informed consent process in a chart note and on any other documents per site SOP. Complete Consent Process Worksheet.
 - ☞ *Consent for specimen storage and possible future research testing is optional. If the participant does not consent, she may still take part in the study.*
6. ____ Update Contact Information and record on local form.
7. ____ Complete the **Screening Summary** form and items 1-1a of the **Enrollment** form.
8. ____ Complete the **Family Planning Methods** form.
9. ____ Administer the **Baseline Genital Symptoms** form.
 - ☞ *This form must be administered prior to random assignment by a staff member who has not previously provided HIV/STI counseling to the participant.*
10. ____ Complete the non-Data Fax **Clinical Eligibility** form
11. ____ Complete web-based Baseline Behavioral Questionnaire.
 - a. ____ Escort participant to the office equipped with a laptop or desktop where the Web-based Baseline Behavioral Questionnaire will be completed.
 - b. ____ Locate the Web page for the Baseline Behavioral Questionnaire (www.scharp.org/MTN004baseline).
 - c. ____ Enter PTID and study code.

Enrollment: Page 3 of 5

PTID:	Visit Date:
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- d. _____ Provide instructions to the participant (if necessary) on how to operate the mouse to respond to questions online.
- e. _____ Select a location for the laptop that is private (i.e., the screen should be out of sight of staff members or other participants while responses are being entered), but allows study staff to be nearby to answer questions or assess whether the participant is having computer problems.
12. _____ Vital Signs and targeted physical (abdominal) exam. Complete **Physical Exam** (non DataFax) and **Pharmacokinetics** form.
13. _____ Perform and document pelvic exam using pelvic exam checklist. Complete the **Screening 1 and Enrollment Pelvic Exam** Data Fax CRF.
14. _____ Collect blood as follows (specimen collection must occur prior to randomization):
- red top tube(s) (no additive)
 - purple top tube(s) (EDTA)
 - blue top tube (Sodium Citrate)
 - green top tube (Lithium Heparin)
15. _____ Complete an **LDMS Specimen Tracking Sheet** for stored samples and/or samples tested at the MTN Network Lab.
16. _____ Prepare blood for testing/storage at the local lab:
- CBC (hemoglobin, hematocrit, RBC, WBC with differential, platelets)
 - Coagulation panel (PT INR and PTT)
 - Liver and renal function (AST, ALT, creatinine level)
 - Lavender top tube (EDTA) for plasma archive (if applicable)
 - Green top tube for SPL7013 level
17. _____ Obtain the next sequential **Clinic Randomization Envelope (or Replacement Envelope, if a replacement participant)**. Assign the next sequential envelope to the participant by completing the row of the appropriate envelope tracking record (Clinic Randomization Envelope Tracking Record or Replacement Envelope Tracking Record) that corresponds to the next sequential envelope.

Enrollment: Page 4 of 5

PTID:	Visit Date:
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18. _____ Open the assigned envelope and confirm that the envelope number printed on the prescription contained in the envelope corresponds with the number on the outside of the envelope.
19. _____ Complete the prescription contained inside the envelope and:
 - Fax a copy of the prescription to the pharmacy and arrange for delivery of the white original prescription to the pharmacy. Retain the envelope and the yellow clinic copy of the prescription in the participant's study notebook. While waiting for gel supplies to be delivered, continue with the remainder of this checklist.
20. _____ Complete items 2-2f of the **Enrollment** form. When gel supplies arrive, complete the remainder of the form.
21. _____ Reinforce the instructions to contact the site to request additional gel, if needed, prior to the next visit and remind the participant to bring her unused applicators to the next visit.
22. _____ Dispense Product and provide study product usage instructions.
23. _____ Instruct participant to insert first dose in study clinic.
24. _____ Reinforce site contact information and instructions to contact the site to report symptoms — *especially genital symptoms* — and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.
25. _____ Explain the weekly follow-up visit schedule to the participant and schedule her phone assessment, 1-Week, 2-Week, and 3-Week study visits at this time.
26. _____ Inform the participant of tests to be performed prior to the next visit. Also inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.
27. _____ Provide study reimbursement.
28. _____ Complete the **Pre-Existing Conditions** form. Record all medical conditions that are ongoing at the time of participant randomization, based on source data collected throughout the screening process. Whenever possible, record a diagnosis rather than individual signs and symptoms. When this is not possible, record each individual sign or symptom. Do not record STIs or other infections that were fully treated prior to randomization. In the "comments" box for each condition, record as much information as possible on the severity and/or frequency of the condition at the time of participant randomization.

Enrollment: Page 5 of 5

PTID:	Visit Date:
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29. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents, including the following non-Data Fax forms:

- Screening 1 Visit Eligibility
- Screening 2 Visit/Enrollment Eligibility
- Baseline Medical History
- History of Genital Symptoms
- Physical Exam
- Pelvic Exam Diagrams
- Clinical Eligibility (from Screening 1 and Enrollment Visits)
- Screening Summary
- LDMS Specimen Tracking Sheet

30. _____ Fax all required Data Fax forms to SCHARP Data Fax:

- Screening Consent
- Demographics
- Screening 1 and Enrollment Pelvic Exam (from Screening 1 and Enrollment Visits)
- Screening 2 Pelvic Exam (if applicable)
- Baseline Genital Symptoms
- STI Laboratory Results*
- Pelvic Laboratory results* (from Screening 1 and Enrollment Visits)
- Safety Laboratory Results* (from Screening 1 and Enrollment Visits)
- Concomitant Medications Log
- Family Planning Methods
- Enrollment
- Pre-Existing Conditions
- Pharmacokinetics

☞ *The STI Laboratory, Pelvic Laboratory, and Safety Laboratory results forms are required for enrolled participants and MUST be completed, reviewed, and faxed to SCHARP when results are available by clinic and/or lab staff.*

Follow-up Clinic Visits: Page 1 of 6

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 1-Week: _____ 2-Week: _____ 3-Week: _____ or Interim: _____ <i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i>	

1. _____ Complete participant registration, confirm the participant's identity, and verify her PTID.
2. _____ Review chart notes and other relevant documentation from previous visit(s).
3. _____ Review elements of informed consent as needed.
4. _____ Explain the content and sequence of procedures for today's visit. Do vital signs and record on the Physical Exam (non-DataFax) form.
5. _____ Provide and explain available exam and lab test results. Provide post-test counseling, if appropriate. Provide treatment for RTIs/STIs if needed. Document treatment on the **Concomitant Medications Log**. Refer to Protocol Appendix II for guidelines on holding, discontinuing or continuing with study gel. Complete **Product Hold/Discontinuation** as necessary. Contact **PSRT** if there are any questions about management.
6. _____ Review/update locator information.
7. _____ Complete/update **Adverse Experience Log** form(s) if required based on interval medical/menstrual history, clinical exams/assessments, and lab tests.
8. _____ Collect ~20 mL urine and:
 - a. _____ Aliquot ~5 mL and perform pregnancy test; retain remaining urine for remainder of visit.
 - b. _____ Complete testing logs and transcribe result onto the form.

If the participant is pregnant:

 - c. _____ Inform the participant that she must discontinue gel use; arrange to collect her unused gel.
 - d. _____ Complete items 1-2 of a **Product Hold/Discontinuation** form.
 - e. _____ Complete a **Pregnancy Report and History** form.
 - f. _____ Complete a **Study Gel Request Slip**, marked "HOLD." Deliver the completed white original to the pharmacy. Retain the yellow clinic copy in the participant's study notebook.
9. _____ Administer the **Family Planning Methods** form.

Follow-up Clinic Visits: Page 2 of 6

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 1-Week: _____ 2-Week: _____ 3-Week: _____ or Interim: _____ <i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i>	

10. _____ **For the 1-Week and 2-Week Visits only:** Administer the **Study Gel Adherence** form
Note: If participant misses her 2-Week Visit, administer this form at the 3-Week Visit.
11. _____ **For the 2-Week Visit only:** Administer the **Acceptability Assessment** form.
Note: If participant misses her 2-Week Visit, administer this form at the 3-Week Visit.
12. _____ **For the 2-Week Visit only:** Administer the web-based **Adherence and Acceptability Questionnaire:**
Note: If participant misses her 2-Week Visit, administer this questionnaire at the 3-Week Visit.
- _____ Escort participant to the office equipped with a laptop or desktop where the Web-based questionnaire will be completed.
 - _____ Locate the Web page for the Acceptability and Adherence Questionnaire (www.scharp.org/MTN004accept)
 - _____ Enter PTID and study code.
 - _____ Remind the participant (if necessary) how to operate the mouse to respond to questions online.
 - _____ Select a location for the laptop that is private (i.e. the screen should be out of sight of staff members or other participants while responses are being entered), but allows study staff to be nearby to answer questions or assess whether the participant is having computer problems.
13. _____ **For the 3-Week Visit only:** Administer the web-based **Study Burden Questionnaire**
Note: If participant terminates the study prior to her 3-Week Visit, administer this questionnaire at the Early Termination Visit.
- _____ Escort participant to the office equipped with a laptop or desktop where the web-based questionnaire will be completed.
 - _____ Locate the web page for the Study Burden Questionnaire (www.scharp.org/MTN004burden).
 - _____ Enter PTID and study code.
 - _____ Remind the participant (if necessary) how to operate the mouse to respond to questions online.
 - _____ Select a location for the laptop that is private (i.e. the screen should be out of sight of staff members or other participants while responses are being entered),

Follow-up Clinic Visits: Page 3 of 6

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>1-Week: ____ 2-Week: ____ 3-Week: ____ or Interim: ____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

but allows study staff to be nearby to answer questions or assess whether the participant is having computer problems.

14. ____ **For the 3-Week Visit only** (or early Termination Visit, if applicable): Complete the **CASI Tracking** form.

15. ____ Administer the **Follow-up Genital Symptoms** form

16. ____ Perform interval medical/menstrual history; record findings on the **Follow-up Medical History** form. Review and update the **Concomitant Medications Log**.
 - a. ____ If genital blood/bleeding is reported, conduct a pelvic exam (if not already required as part of the visit). Complete a **Genital Bleeding Assessment** form for unexpected genital bleeding.
 - b. ____ If applicable, review the status of previously-reported adverse events and update previously-completed **Adverse Experience Log** forms.

17. ____ Perform pelvic exam per the Follow-Up Pelvic Exam Checklist. During exam, if applicable, assess genital symptoms reported during administration of the **Follow-up Genital Symptoms** form. Provide or refer for follow-up care as needed. Document follow-up in chart notes.

18. ____ If applicable, assess any non-genital symptoms reported in the participant's interval medical/menstrual history. Provide or refer for follow-up care as needed. Document follow-up in chart notes.

19. ____ **1-Week Visit Only:** For all participants (unless product is held):
 - a. ____ Administer the **Gel Re-Supply Worksheet**.
 - b. ____ Complete a **Study Gel Request Slip**.
 - c. ____ Fax a copy of the Study Gel Request Slip to the pharmacy. Arrange for delivery of the white original to the pharmacy. Retain the yellow clinic copy in the participant's study notebook.
 - d. ____ While waiting for gel supplies to be delivered, continue with the remainder of this checklist. After gel supplies are received, provide the supplies to the participant and document the number of cartons provided here →

Follow-up Clinic Visits: Page 4 of 6

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>1-Week: _____ 2-Week: _____ 3-Week: _____ or Interim: _____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

20. _____ If gel use is held/discontinued or resumed at this visit, document the rationale for the hold/discontinuation or resumption in chart notes and/or on other applicable source documents. Also document the hold/discontinuation or resumption on a Product Hold/Discontinuation form a Study Product Request Slip. Deliver the white original Study Product Request Slip to the pharmacy; retain the yellow clinic copy in the participant's study notebook.
21. _____ Collect blood as follows (if interim visit, collect any specimens as clinically indicated):
- red top tube(s) (No additive)
 - purple top tube(s) (EDTA)
 - blue top tube (Sodium Citrate)
 - green top tube (Lithium Heparin) (2-Week Visit only; collect at 3-Week Visit *only* if participant has missed 2-Week Visit)
22. _____ **For the 2-Week Visit only:** Complete the **Pharmacokinetics** DataFax form
23. _____ Complete an **LDMS Specimen Tracking Sheet** for stored samples and/or samples tested at the MTN Network Lab.
24. _____ Prepare blood for testing/storage at the local lab:
- CBC (hemoglobin, hematocrit, RBC, WBC with differential, platelets)
 - Coagulation panel (PT INR and PTT)
 - Liver and renal function (AST, ALT, creatinine level)
 - Lavender top tube (EDTA) for plasma archive (if applicable)
 - Green top tube for SPL7013 level
25. _____ Complete **Follow-up Visit** form (or **Interim Visit** form, if an interim visit)
26. _____ Provide condoms, other applicable prevention supplies (if any), and/or referrals if needed/requested.
27. _____ Inform the participant of tests to be performed prior to the next visit. Also inform the participant of availability of HIV/STI counseling, testing, and STI treatment for partners.

Follow-up Clinic Visits: Page 5 of 6

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>1-Week: ____ 2-Week: ____ 3-Week: ____ or Interim: ____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

- 28. ____ Provide HIV/STI and/or adherence counseling if needed/requested.
- 29. ____ Reinforce availability of HIV/STI counseling, testing, and potential STI treatment for partners.
- 30. ____ 1-Week Visit only: Reinforce the study product usage instructions, and instructions to contact the site to request additional gel, if needed, prior to the next visit, and remind the participant to return unused applicators at the next visit.
- 31. ____ Reinforce site contact information and instructions to contact the site to report symptoms — especially genital symptoms — and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.
- 32. ____ Provide study reimbursement and schedule next visit (if indicated).

Additionally Only If Clinically Indicated (C1-C3):

C1. ____ Perform dipstick urinalysis on aliquot of urine used for pregnancy testing. Complete testing logs and transcribe results onto the **STI Laboratory Results** form.

C1a. ____ If clinically indicated, conduct urine culture and sensitivity, and provide treatment per site SOP. Document additional work-up in chart notes. Document treatment on the **Concomitant Medications Log**. Document urine culture result on the **STI Laboratory Results** form and urine sensitivity results in the participant's chart notes.

C2. ____ Transfer remaining (15 mL) urine to conical tube or transfer directly into a Genprobe Transport tube and refrigerate pending delivery to the local lab for shipment to the Network Lab for gonorrhea and chlamydia Genprobe Aptima.

C3. ____ Collect and prepare blood for syphilis serology at the local lab.

- 31. ____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents for the visit, including the following non-Data Fax forms:
 - Follow-up Medical History
 - Pelvic Exam Diagrams

Follow-up Clinic Visits: Page 6 of 6

PTID:	Visit Date:
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Please indicate to which follow-up visit this checklist applies:

1-Week: ____ 2-Week: ____ 3-Week: ____ or Interim: ____

Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.

- Gel Re-Supply Worksheet (if study gel dispensed)
- Study Gel Request Slip (if study gel dispensed)
- Participant Replacement Assessment Worksheet

32. ____ Fax all required Data Fax forms to SCHARP Data Fax:

- Follow-up Visit or Interim Visit
- Family Planning Methods
- Follow-up Pelvic Exam
- Follow-up Genital Symptoms
- Pelvic Laboratory Results
- Safety Laboratory Results (when all results available)
- STI Laboratory Results (if clinically indicated)
- Study Gel Adherence (Weeks 1 and 2)
- Acceptability Assessment (Week 2)
- Pharmacokinetics (Week 2)
- CASI Tracking (Week 3 or Early Termination Visit)

As indicated:

- Concomitant Medications Log (required for updated or new pages)
- Adverse Experience Log (required if any AEs identified or updated at this visit)
- Product Hold/Discontinuation (required if product use held/discontinued or resumed at this visit)
- Pregnancy Report and History (required if pregnancy identified at this visit)
- Pregnancy Outcome (required if pregnancy outcome ascertained at this visit)
- HSV-2 Culture

Scheduled or Early Termination:

- Termination
- End of Study Inventory

Follow-up Pelvic Exams: Page 1 of 3

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>1-Week: _____ 2-Week: _____ 3-Week: _____ or Interim: _____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit..</i></p>	

1. _____ Review chart notes and other relevant documentation from previous visit(s).
2. _____ Using a pencil, write the PTID and specimen collection date on the frosted side of four microscope slides (2 for vaginal wet mount and 2 for vaginal Gram Stain). Then affix a SCHARP-provided PTID label to the other side of each slide (under the pencil markings) and write the specimen collection date in ink on each label.
3. _____ Affix a SCHARP-provided PTID label to a glass or plastic tube containing approximately six drops (100 μ L) of saline. Write the specimen collection date in ink on the label.
4. _____ Explain the exam procedures to the participant and answer any participant questions.
5. _____ Position and drape the participant comfortably.
6. _____ Palpate inguinal lymph nodes. Document abnormal findings on the **Follow-up Pelvic Exam** form.
7. _____ Inspect external genitalia. Note all findings on the Pelvic Exam Diagrams. Document abnormal findings in items 1-1a on the **Follow-up Pelvic Exam** form.
8. _____ Insert speculum, using warm water as lubricant if needed. Observe general state of the cervix.
9. _____ Assess for homogenous discharge. Record observation on the **Pelvic Laboratory Results** form.
10. _____ Place pH strip against the lateral vaginal wall until moistened. Alternatively, collect vaginal fluids from the lateral vaginal wall via swab and swab fluids onto the pH strip. Record on the **Pelvic Laboratory Results** form.

Follow-up Pelvic Exams: Page 2 of 3

PTID:	Visit Date:
Please indicate to which follow-up visit this checklist applies: 1-Week: _____ 2-Week: _____ 3-Week: _____ or Interim: _____ <i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i>	

11. _____ Swab vaginal fluids from the lateral vaginal wall for Gram stain; do not place the swab in saline, transport medium, or a transport container prior to slide preparation (see also SSP Section 12.)
 - 11a. _____ Roll the swab across two labeled slides and then allow the specimens to air dry.
 - 11b. _____ Document specimen collection on the **Follow-up Pelvic Exam** form and on the **LDMS Specimen Tracking Sheet**

12. _____ Swab vaginal fluids from the lateral vaginal wall for wet prep; proceed immediately to Step 12a or placed the swab in a glass or plastic tube containing approximately six drops (100 μ L) of saline to allow for non-immediate slide preparation and evaluation, as follows (see also SSP Section 12.)
 - 12a. _____ Smear vaginal fluids from the swab onto two labeled slides.
 - 12b. _____ Apply KOH to one slide, perform whiff test, then apply cover slip.
 - 12c. _____ Apply saline to the second slide, emulsify, and apply cover slip. Immediately evaluate for trichomonads, yeast buds, pseudohyphae, and clue cells.
 - 12d. _____ Evaluate KOH slide for yeast buds and pseudohyphae.
 - 12e. _____ If slides are read in-clinic by clinical staff, record results directly onto the **Pelvic Laboratory Results** form. If slides are read by lab staff (either in the local lab or a designated in-clinic lab area) complete testing logs and then transcribe results onto the **Pelvic Laboratory Results** form.

13. _____ Collect quantitative vaginal culture. Document specimen collection on the **Follow-up Pelvic Exam** form and on the **LDMS Specimen Tracking Sheet**.

14. _____ Inspect cervix and vagina:
 - 14a. _____ Naked eye exam \Rightarrow Note all findings on the Pelvic Exam Diagrams. Document abnormal findings in items 1-1a on the **Follow-up Pelvic Exam** form. If colposcopy is not done, document degree of cervical ectopy on the **Follow-up Pelvic Exam form**.

Follow-up Pelvic Exams: Page 3 of 3

PTID:	Visit Date:
<p>Please indicate to which follow-up visit this checklist applies:</p> <p>1-Week: _____ 2-Week: _____ 3-Week: _____ or Interim: _____</p> <p><i>Note: Any protocol-specified studies or exams that were not completed on the assigned visit date must be completed at the next scheduled visit or at an interim visit.</i></p>	

15. _____ If bleeding, blood, and/or blood-tinged discharge are observed, refer to SSP Section 10.6 and, if indicated, complete a **Genital Bleeding Assessment** form.
16. _____ Collect cervical swabs for cytokines and innate factors. Document specimen collection on the **Follow-up Pelvic Exam** form and on the **LDMS Specimen Tracking Sheet**.
17. _____ If one or more genital ulcers are observed:
- 17a. _____ Swab each ulcer. If a cluster of ulcers is observed, each ulcer in the cluster should be sampled with the same swab. Otherwise a different swab should be used for each ulcer.
- 17b. _____ Place (each) swab in a cryovial labeled with a SCHARP-provided PTID label.
- 17c. _____ Document specimen collection on the **Follow-up Pelvic Exam** form and the **LDMS Specimen Tracking Sheet**.
18. _____ **2-Week Visit only** (if indicated at all other visits): Colposcopic exam ⇒ Note all findings on the Pelvic Exam Diagrams. Document abnormal findings and degree of cervical ectopy on the **Follow-up Pelvic Exam** form. Save image(s) of abnormalities electronically (optional). Normal images also may be saved.
19. _____ Perform bimanual exam. Document abnormal findings on the **Follow-up Pelvic Exam** form.

Section 8. Participant Retention

This section presents information related to definitions, requirements, and procedures for participant retention in MTN 004.

8.1 Retention Definition

The term “retention” generally refers to completion of follow-up visits and procedures as specified in a study protocol. This definition must be operationalized for any study, and operational definitions usually reflect the primary objectives and endpoints of a study.

- During the study, retention for scheduled follow-up visits will be defined based on whether participants complete scheduled visits within the target visit window. Participants who complete their scheduled visits within the target visit window will be considered “retained” for those visits.

As indicated above, participants who do not complete a particular scheduled visit within the target window, but then complete the next scheduled visit, will not be considered retained for the missed visit, but will be considered retained for the next scheduled visit. Thus retention rates can fluctuate over time and across visits. Importantly, retention shortfalls can be made up by ensuring that participants return for their next scheduled visit after missing a visit.

The MTN Statistical and Data Management Center (SDMC) will generate reports during the study presenting retention rates for key study visits designated by the Protocol Team. The SDMC also will generate a final end-of-study retention rate for each site after the study is completed. For purposes of monitoring and ongoing retention efforts at each site, retention will be defined in SCHARP reports as described below:

Retained On-Time: Participant completed visit within the target visit window and thus meets the protocol definition of “retained” for that visit.

Retained Early or Late: Participant completed a visit, but was outside the target visit window. All visit procedures should be conducted for the given visit. The visit will not meet the protocol definition of “retained,” as the visit occurs outside the visit window; however, the visit will be counted as “early” or “late” retained and will contribute to the site’s overall retention as reflected in the SCHARP reports. Below are some examples of “early” and “late” retained visits:

- A participant missed her One-Week Visit and the visit window (day 6-8 post enrollment) has passed. The participant then shows up for the visit on day 9. All One-Week Visit procedures should be done at this time, and the visit should be assigned the same visit code (03.0) as the One-Week Visit. The visit will be counted as a “late retained visit” based on the visit date recorded on the CRFs.
- A participant knows in advance that she will be unable to complete her Two-Week visit within the visit window (day 13-15 post enrollment), but is available for a visit one day before the window opens (day 12). In this case, the participant should be asked to complete the visit early, before the visit window opens; the visit should be assigned the same visit code (04.0) as the Two-Week Visit. This visit will count as an “early retained visit” based on the visit date recorded on the CRFs.

See section 14 of this SSP manual for more details on assigning interim visit codes.

8.2 Retention Requirements

Each study site will target retention of at least 95% of enrolled study participants at the Three-Week study visit (day 20-24 post enrollment).

The purpose of the 95% annual retention target is to ensure the accuracy of study results. Low retention rates can have a serious impact on the accuracy of study outcomes. In each group, the observed safety/toxicity and adherence/acceptability rates could be higher or lower than the true rate, but it is not possible to determine the direction of the error. To avoid this problem, and thereby avoid bias in the study results, high participant retention rates must be maintained throughout the study.

To aid in retention, sites are advised to develop a participant tracking database or alternative method of tracking participant visits and visit windows. All on-site databases must be secured with password-protected access systems. Any lists, logbooks, appointment books, or other documents that link PTIDs to other participant identifiers must be stored securely in a location separate from records identified by either participant name only or PITD only. When in use, these documents must not be left unattended or otherwise accessible to study participants, other study clinic patients, or any other unauthorized persons.

8.3 Retention SOPs

Site staff is responsible for establishing a standard operating procedure (SOP) for participant retention, and for updating the SOP and retention efforts undertaken to meet the study retention goal of 95% at 3 weeks of follow up. The SOP should minimally contain the following elements:

- Site-specific retention goals
- Methods for tracking actual retention versus retention goals
- Procedures for completing and updating participant contact information
- Site-specific definition of “adequate” contact information
- Visit reminder methods and timeframes
- Methods and timeframes for identifying when a visit has been missed
- Planned retention methods, including what outreach/locator efforts are taken within 24 hours after a missed visit
- Methods for timely evaluation of the utility of retention methods
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

8.4 Obtaining and Updating Contact Information

Successful retention begins with collection of contact information from each study participant. All study participants will be asked to provide contact information during the study screening process, and to continually review/update this information during follow-up. Each site must specify its definition of adequate contact information in its retention SOP.

Each study site is encouraged to develop an exhaustive contact form which may include:

- Participant's full name, alias, and/or nickname; government-issued identification number; home address; home phone number; mobile phone number; pager number; work address; work phone number; fax number; e-mail address; daytime and nighttime locations, meeting places, hangouts.
- Name, address, telephone number, and/or other contact information for stable community contacts (i.e., participant family members and friends) who typically know the whereabouts of the participant.

Note: Although contact information for a participant's current primary partner likely will be useful, contact information for other contacts should also be collected, since the participant's relationship with this partner could change during the course of the study.

- Name, address, telephone number, and/or other contact information for the participant's health care provider, school or training program; church or other place of worship; social service case worker; counselor, rehabilitation provider, etc.; participant's child's school and health care provider.
- Name, address, telephone number, and/or other contact information for support groups, shelters, food pantries, and other social service organizations used by the participant.

During the informed consent process and when collecting contact information, study participants must be informed that their contact sources will be contacted if study staff are unable to locate the participant directly. Study staff will negotiate with the participant how they will identify themselves when contact sources are contacted. Arrangements agreed upon with the participant should be documented on the contact form.

Study staff should view every participant contact as an opportunity to update the participant's contact information. When updating contact information, actively review each item on the contact form to determine whether the information is still current (i.e., rather than simply asking "Has any of your information changed since your last visit?"). Also probe for additional information that the participant was not able or willing to provide at previous visits.

8.5 Retention Tips

Some tips for successful retention are as follows:

- Dedicate adequate staff time and effort to retention efforts.
- Work with community members to identify the most applicable contact and retention strategies for the local study population, including the type and amount of participant incentives.

- Keep participants and community members up-to-date on study progress to foster a sense of partnership and ownership of the study (through the use of participant newsletters, for example).
- Inform local service providers who interact with the local study population about the study, so that they also can express their support for the study.
- Emphasize the value of the participant’s involvement in the study during the study informed consent process and subsequently at follow-up visits. When participants complete scheduled visits, acknowledge and commend their commitment, time, and effort devoted to the study.
- Host gatherings, parties and/or other social events for participants.
- Host social, educational, and/or other “male involvement” events for participants’ partners.
- Use tracking tools to identify when participants’ scheduled visits are due and/or overdue. Establish routine mechanisms to remind both study staff and participants of upcoming scheduled visits.
- Schedule all follow up visits at the participant’s Enrollment Visit. Thereafter, at each follow up visit, confirm the scheduling of the next visit and give the participant an appointment card with the scheduled visit date and time noted.
- Prepare a calendar of scheduled visits (and anticipated time of menses) for each enrolled participant, based on her enrollment date, or offer a planner/calendar as an incentive and note all study appointments in the planner/calendar. Note the dates of all scheduled visits in the participant’s file for easy reference
- Contact participant or ask participant to contact the site around the time of participant’s menses to confirm next appointment and verify date of the visit will not occur during menses.
- For participants who demonstrate a pattern of late or missed appointments, schedule follow-up visits for the beginning of the target visit window (i.e., at the earliest date in the visit window) to allow maximum time for re-contact and re-scheduling if needed.
- Pay close attention to the target visit window and prioritize retention efforts for participants nearing the end of the window. Organize daily caseloads and work assignments based on these priorities.
- Follow-up on missed appointments with an attempt to re-contact/re-schedule within 24 hours (preferably on the same day). Continue these efforts per the local retention SOP until contact is made.
- Keep contact information up-to-date and maintain thorough documentation of all efforts to contact the participant. Keep all this information in an organized manner, so that different staff members can easily review the information and contribute to re-contact efforts when necessary.
- Make use of all available contact methods (e.g. phone, mail, home visits, street outreach, newspapers, e-mail/internet). Also make use of other available contact information sources, such as phone and postal directories and other public registries.

- Post outreach workers at other local service organizations used by the study population.
- Attempt contact with the participant at different times during the day and the week, including evenings and weekends.
- If a participant reports that she wishes to discontinue participation in the study, ask if she would be willing to complete a final visit at the end of the study. If the participant refuses this level of involvement, explain that she is always welcome to come back if she wishes.

Section 9. Study Product Considerations for Non-Pharmacy Staff

Attention: This section provides information and instructions for non-pharmacy staff related to the ordering, transport, and delivery of MTN 004 study products for study participants. Record keeping requirements for non-pharmacy staff also are provided. Please also refer to related information in Sections 4 and 6 of this manual.

9.1 Responsibilities and Obligations with Regard to Blinding

MTN 004 Investigators of Record (IoRs), and by delegation all MTN 004 study staff, are responsible for maintaining the integrity of the study's blinded design. All Protocol Team members and study participants, without exception, will not be provided information on the identity of the specific study gel (VivaGel®, VivaGel® placebo or HEC placebo gel) to which participants have been assigned. The Pharmacist of Record (PoR) at all sites will be blinded to all treatment assignments. Access to study pharmacy facilities, and all study gel supplies and documentation stored in these facilities, is limited to study pharmacy staff only. The IoR or designee must ensure the security of study pharmacy facilities by empowering the MTN 004 PoR to control access to these facilities and all study gel supplies and documentation stored therein.

Blinding will be maintained throughout the study and until all study endpoint data have been verified and are ready for final analysis. There are no circumstances under which it is expected that unblinding will be necessary to protect the safety of study participants. In the event that study staff becomes concerned that a participant may be put at undue risk by continuing use of her assigned study gel, the IoR or designee may discontinue study gel use by the participant. Knowledge of the specific study gel to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an IoR or designee feels that study gel-specific information is necessary to protect participant safety, he/she should notify the MTN 004 Protocol Safety Review Team (PSRT).

Additional operational requirements to preserve blinding are as follows:

- Clinic staff should respond to participant questions about how to store gel supplies and use gel applicators. Sample gel cartons and applicators (provided by the MTN CORE) should be stocked at all clinic locations for educational/training/counseling purposes. Actual study products may not be used for educational/training/ counseling purposes.
- Clinic staff may observe the participant remove the first dose from the carton and observe the participant administer the gel.
- Clinic staff may observe or handle individual wrapped gel applicators for purposes of counting the number of returned unused applicators (to document on the CRF).
- All study locations should be stocked with suitable biohazard containers, provided by the Network Lab, in which to store unused applicators that participants may bring with them to the Two-Week Clinic Visit. (see Section 9.6. for further information related to unused applicators).
- After administration of the first dose at the site, under no circumstances should clinic staff dispense gel from any applicators. These restrictions also apply to pharmacy staff, unless specific instructions to inspect or examine applicators are received from the MTN Pharmacist.
- In the event that a participant reports damage to her gel supplies, difficulty using her applicators, or other issues or problems with her applicators or gel — other than signs, symptoms, or other adverse events associated with gel use — clinic staff should refer the participant to the PoR to further discuss and evaluate her report or concern.

- If the participant's applicators have been damaged, the PoR will collect the damaged supplies from the participant (if she has brought them with her) and dispense replacement supplies for her as ordered by site clinic staff.
- If the PoR determines that the participant requires additional instruction on how to use the applicators, he/she will refer the participant back to clinic staff for refresher instruction.
- If the PoR identifies problems with the participant's applicators or gel, the PoR will immediately inform the MTN Pharmacist of the problem and take action per instructions received from the MTN Pharmacist. The MTN Pharmacist will inform the Pharmaceutical Co-Sponsors, MTN CORE (FHI), DPT and Brecon Pharmaceuticals Ltd.

The PoR will document his/her interactions with participants, and subsequent action taken, in signed and dated notes that are retained in participant-specific pharmacy files. The PoR will forward photocopies of his/her notes — and/or other forms of documentation — to clinic staff to ensure timely clinic staff awareness of the resolution of participant reports. If circumstances require the PoR to dispense replacement gel supplies to a participant, the PoR will need to obtain an MTN 004 Replacement Prescription from site clinic staff.






9.2 Gel Use Instructions

Participants will be instructed to insert one applicatorful of study gel – the entire contents of one applicator – into the vagina twice daily, in the morning and in the evening. The evening dose should be administered at bedtime or longest period of rest. Detailed instructions for insertion of study gel are listed in Figure 9-1 below. These instructions will be translated into Spanish at the Puerto Rico site, and will be illustrated to optimize participants' understanding of them. A listing of frequently asked study gel use questions, and answers to these questions, is provided in Section Appendix 9-1.

Figure 9-1

Study Gel Use Instructions for MTN 004

Participants: Insert one dose of study gel – the entire contents of one applicator – into the vagina twice daily, once in the morning and again in the evening just before the longest period of rest (about 12 hours after the morning dose).

<p>1. Removing the Applicator:</p> <ul style="list-style-type: none">• Tear open the opaque, plastic wrapper and remove the applicator which is already pre-filled with gel• Remove the applicator and plunger• Place the small end of the plunger in the hole at the back end of the applicator (opposite the blue cap)• Unscrew the blue cap  <p>2. Inserting the Applicator:</p> <ul style="list-style-type: none">• Choose a comfortable position, for example standing with one leg raised, squatting with your feet apart, or lying on your back with your knees apart 	<ul style="list-style-type: none">• Hold the applicator with your thumb and middle finger about half-way along the barrel  <ul style="list-style-type: none">• Gently slide the applicator into your vagina until your fingers touch your body. Half of the barrel of the applicator should go inside your body. The other half should stay outside the body• While holding the applicator in place, push the plunger until it stops  <ul style="list-style-type: none">• Withdraw the applicator from your vagina <p>3. Follow up Information:</p> <ul style="list-style-type: none">• Discard the used applicator, wrapper, and blue cap  <ul style="list-style-type: none">• Bring all unused, wrapped, study gel applicators to your next visit
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Note: Study Staff should inform participants that they may experience some minor gel leakage from the vagina, when inserting the filled applicator into the vagina.

9.3 MTN 004 Study Gel Re-Supply Worksheet

The MTN 004 Study Gel Re-Supply Worksheet (Figure 9-2) is an operational tool and source document designed to assist clinic staff in calculating the quantity of study gel to be ordered (and dispensed by study pharmacy staff) at a given study follow-up visit for participants.

At the Enrollment Visit, clinic staff will instruct participants to bring all unused study gel applicators to the site clinic at their One-Week Clinic Visit, when new study gel supplies will be dispensed (unless study gel is held or permanently discontinued). At the One-Week Clinic Visit, clinic staff will instruct participants to continue to use any unused, wrapped (unopened) study gel applicators in their possession (from study gel cartons dispensed at enrollment), and to use applicators from the new study gel supplies (dispensed at the One-Week Clinic Visit), until they come in for the Two-Week Visit. Clinic staff will instruct participants to return all unused study gel applicators in her possession to the Two-Week Clinic Visit. If a participant does not return the study gel applicators in her possession at the Two-Week Clinic Visit, clinic staff will make every effort to collect the study gel applicators at the participant's Three-Week Clinic Visit, or as soon as possible thereafter.

Figure 9-2

Statistical Center for HIV/AIDS Research & Prevention (SCHARP)

MTN 004 Study Gel Re-supply Worksheet

MTN 004 (136)

Page 1 of 1

Participant ID

Site Number			Participant Number				Chk	

Visit Date

dd		MMM		yy	

Clinic Staff: Study gel is dispensed as 10 applicators per carton. Review items 1–5a with the participant.

1. Number of days until participant's next scheduled study visit: # of days → Multiply by 2: applicators needed

2. Number of unused, **wrapped** applicators in participant's possession: unused, **wrapped** applicators

3. Subtract item 2 from item 1: = applicators to dispense

→ **If 0 or a negative number, do not dispense any cartons. Go to item 5.**

4. Number of cartons to dispense: # cartons to dispense

Note: If the number in item 3 (the number of applicators to dispense) is > 0 but ≤ 10, order 1 carton to be dispensed. If the number in item 3 (the number of applicators to dispense) is > 10, order 2 cartons to be dispensed. Complete a Study Gel Request Slip to order the first carton to be dispensed at this visit. If ordering a second carton to replace a carton that was dispensed at a previous visit, open the appropriate Replacement Envelope and complete the Replacement Prescription form for the second (replacement) carton. Inform the participant of the number of cartons to be dispensed to her today.

5. Did the participant report that her applicators were used other than as directed, or that anything else happened to any of her applicators (e.g., they were lost or damaged) since the last visit? yes no → **If no, end of form.**

5a. Describe what happened, number of applicators involved, and any follow-up discussion with the participant:

Version 1.0, 20-MAR-07

N:\mnt\protocols\MTN004\Product&randomization\Gel_resupply\m004_studygel_resupply_worksheet.fm

0	1
Language	

Staff Initials / Date

9.4 MTN 004 Study Gel Request Slip

The MTN 004 Study Gel Request Slip (Figure 9-3) should be used by clinic staff to communicate to pharmacy staff:

- The number of cartons to be re-supplied to each participant at each visit. At the One-Week Clinic Visit participants should usually require one carton of study product. If more than one carton is needed, the first carton would be requested with Study Gel Request Slip. To request an additional carton(s) (e.g., to replace a previously dispensed carton) a Replacement Envelope must be opened and the replacement Prescription form completed. **Note: the MTN 004 Study Gel Request Slip should not be completed to order replacement cartons (e.g., for previously dispensed cartons that are lost or damaged).**
- Clinic staff decisions to hold study gel use for a participant, to resume study gel use after a prior hold, or to permanently discontinue study gel use
- The cartons being ordered are for a replacement participant.

The MTN 004 Study Gel Request Slip is a two-part no carbon required (NCR) document that is available in pads of 50 and provided by the SDMC. In the event that clinic staff requires additional pads, they should contact the Protocol Pharmacist and SDMC Project Manager for a resupply. Complete the Study Gel Request Slip as follows:

- Record the clinic name at the top of the slip. The name recorded must be identical to the clinic name listed on the site's randomization envelopes and prescriptions, unless an alternative clinic name or abbreviation is designated in the site SOP for study gel re-supply during follow-up.
- Record the PTID and the number of the Clinic Randomization Envelope (or Replacement Randomization Envelope, for replacement participants) assigned to the participant in the boxes provided.
- Mark the box for either "RE-SUPPLY," "HOLD," "PERMANENT DISCONTINUATION" or "RESUME" to indicate the action to be taken in the study pharmacy. When marking "RE-SUPPLY" or "RESUME," record the number of cartons of study gel to be dispensed to the participant.
 - When "RE-SUPPLY" is marked, study gel will be dispensed for the participant in the quantity entered on the slip.
 - When "HOLD" is marked, study gel will not be dispensed for the participant unless/until another slip marked RESUME is subsequently completed and received in the pharmacy.
 - When "PERMANENT DISCONTINUATION" is marked, no study gel will be dispensed to the study participant starting from the point the Study Gel Request Slip is received in the pharmacy.
 - When "RESUME" is marked, a previous hold will end, and study gel will be dispensed for the participant in the quantity entered on the slip. A signed, dated photocopy of the chart note documenting the original purpose for HOLD should be attached to the Study Gel Request Slip marked "RESUME."

- The clinic staff name, signature, and signature date must be completed on the same day as the participant’s visit by a clinic staff member authorized to order study gel supplies for participants during follow-up. DAIDS does not require that an authorized prescriber sign and date the Study Gel Request Slips; however site-specific pharmacy regulations may be more stringent than DAIDS requirements. All sites must comply with local requirements.

Double-check the accuracy of all entries and then separate the two parts of the completed Study Gel Request Slip. Retain the yellow copy (labeled “Clinic”) in the participant study notebook. Deliver the white original (labeled “Pharmacy”) to the study pharmacy in the same manner that original prescriptions are delivered to the pharmacy. Both the original and clinic copy of the slip may be hole-punched.

Figure 9-3

MTN 004 Study Gel Request Slip

Clinic Name: _____	Randomization Envelope # <input type="text"/> <input type="text"/> <input type="text"/>
Participant ID <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/>	First Randomization Code <input type="text"/> <input type="text"/> <input type="text"/> Second Randomization Code <input type="text"/> <input type="text"/> <input type="text"/> N/A <input type="checkbox"/>
Clinic Staff Instruction: Mark whether this is a study gel re-supply, hold, resume, or permanent discontinuation request. Record the number of study gel cartons to be dispensed (if applicable), and sign and date. Deliver the original white copy (labeled “Pharmacy”) to the pharmacy. File the yellow copy (labeled “Clinic”) in the participant study notebook.	
<input type="checkbox"/> RE-SUPPLY Pharmacy: Dispense <input type="text"/> cartons of study gel (10 applicators per carton).	
<input type="checkbox"/> HOLD Pharmacy: Do not dispense study gel to participant unless another MTN 004 Study Gel Request Slip marked “Resume” is received.	
<input type="checkbox"/> RESUME Pharmacy: Dispense <input type="text"/> cartons of study gel (10 applicators per carton) as authorized by the Investigator of Record and/or designated clinic staff.	
<input type="checkbox"/> PERMANENT DISCONTINUATION Pharmacy: Do not dispense any further study gel to participant.	
Clinic Staff Name (please print): _____	
Clinic Staff Signature: _____	
Date: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
Pharmacy	

9.5 Dispensing Study Gel During On-Site Visits

Refer to Section 4 of this manual for further information on procedures for participant randomization, initial ordering and dispensation of study gel for enrolled study participants. Detailed instructions for completing MTN 004 Prescriptions, and MTN 004 Replacement Prescriptions are provided in Section 4

Upon receipt of a completed and signed MTN 004 Prescription at the Enrollment Visit (or MTN 004 Replacement Prescription for replacement participants), pharmacy staff will dispense study gel supplies.

Gel supplies will be dispensed in cartons containing ten (10) identically-packaged, individually-wrapped, pre-filled applicators each. Two cartons, containing (20 applicators), will be dispensed at the Enrollment Visit. At the One-Week Visit (or at interim visit(s), for participants who need replacement gel, site clinic staff will complete the Study Gel Re-supply Worksheet and order study gel supplies in quantities expected to be sufficient until the participant's next follow-up visit. It is anticipated that most participants will receive one additional carton (10 applicators) of study gel at the One-Week Clinic Visit. Cartons will be sealed with tamper-evident tape and labeled by the PoR in accordance with US and local requirements. In all cases, carton labeling will include a randomization code.

Participant-specific study gel cartons may be dispensed to participants in one of three ways:

- From the pharmacy directly to the participant
- From the pharmacy to authorized clinic staff who will then deliver the cartons to the participant
- From the pharmacy to authorized transport staff (or “runners”) who will transfer the cartons to authorized clinic staff who will then deliver the cartons to the participant
- Each study site must designate its dispensing method in the MTN 004 standard operating procedures (SOPs) for participant randomization and gel re-supply during follow-up. These SOPs should be developed with input from both pharmacy and clinic staff. They must be approved by the MTN Pharmacist prior to study activation and may only be modified after consultation with the MTN Pharmacist. Further information related to each method is provided in Sections 9.5.1-9.5.3 below.

9.5.1 Dispensing from the Pharmacy Directly to Participants

At sites choosing to dispense study gel cartons directly from the pharmacy to participants, prescriptions and Study Gel Request Slips are expected to be delivered to the pharmacy by the participants themselves, although this may be done by clinic staff or a runner. Upon receipt of a completed and signed prescription or Study Gel Request Slip, the PoR will prepare the number of participant-specific study gel cartons entered on the prescription or request slip. Cartons may be prepared based on either original documents or faxed copies, but cartons will not be released to participants until the original prescription or original Study Gel Request Slip is received by the site pharmacy.

9.5.2 Dispensing from the Pharmacy to Clinic Staff

At sites choosing to dispense gel cartons to clinic staff who will then deliver the cartons to participants, prescriptions and Study Gel Request Slips are expected to be delivered to the pharmacy by clinic staff or a runner. Upon receipt of a completed and signed prescription or Study Gel Request Slip, the PoR will prepare the number of participant-specific study gel cartons entered on the prescription or slip. Cartons may be prepared based on either original documents or faxed copies, but cartons will not be released to clinic staff until the original prescription or request slip is received by the site pharmacy.

The MTN 004 Record of Receipt of Participant-Specific Gel Cartons (see Section Appendix 9-2) must be used to document dispensing of participant-specific study gel cartons to clinic staff. Pharmacy staff will complete the top section (site name, clinic name) and the first four columns on the Record of Receipt. When receiving study gel cartons from the pharmacy, clinic staff will verify the PTIDs, confirm the number of cartons received for each PTID, and complete the remaining three columns on the Record of Receipt for

each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the pharmacy.

Clinic staff are responsible for controlling access to the gel cartons dispensed into their custody and ensuring that the cartons are delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of the cartons to designated participants in the participants' study charts. Delivery may be documented in chart notes, on visit checklists, or on other source documents designated for this purpose by clinic staff. In the event that all gel cartons dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the remaining cartons to the pharmacy as soon as the participant's visit is completed.

9.5.3 Dispensing from the Pharmacy to Runners for Further Transfer to Clinic Staff

At sites choosing to dispense gel cartons to runners who will transfer the cartons to clinic staff for subsequent delivery to participants, prescriptions and Study Gel Request Slips are expected to be delivered to the pharmacy by a runner. Upon receipt of a completed and signed prescription or Study Gel Request Slip, the PoR will prepare the number of participant-specific study gel cartons entered on the prescription or slip. Cartons may be prepared based on either original documents or faxed copies, but cartons will not be released to a runner until the original prescription or request slip is received by the site pharmacy.

The MTN 004 Record of Receipt of Participant-Specific Gel Cartons (see Section Appendix 9-2) must be used to document dispensing of participant-specific study gel cartons to runners. MTN 004 Daily Runner Logs (see Section Appendix 9-3) must be used to document transfer of participant-specific study gel cartons from runners to clinic staff.

Pharmacy staff will complete the top section (site name, clinic name) and the first four columns on the Record of Receipt. When receiving study gel cartons from the pharmacy, runners will verify the PTIDs, confirm the number of cartons received for each PTID, and complete the remaining three columns on the Record of Receipt for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the pharmacy.

At the beginning of each work day, runners will complete the top section (site name, clinic name, date) of their Daily Runner Logs. When receiving study gel cartons from the pharmacy, in addition to completing the Record of Receipt for each PTID, runners will complete the first three columns on the Daily Runner Log for each PTID.

Runners are expected to deliver participant-specific gel cartons to authorized clinic staff directly after collecting the cartons from the pharmacy. Runners must control access to the cartons dispensed into their custody and deliver the cartons only to authorized clinic staff. Runners also must retain and control access to their Daily Runner Logs until the logs are returned to the pharmacy, at which time pharmacy staff assume responsibility for the logs. If completed logs are not returned to the pharmacy by the end of each work day, the PoR will notify appropriate clinic or pharmacy supervisory staff (per site SOPs) to ensure timely recovery of the logs. If completed logs are not recovered and delivered to the pharmacy within five calendar days, the PoR will notify the MTN Pharmacist via email.

When receiving study gel cartons from runners, clinic staff will verify the PTIDs, confirm the number of cartons received for each PTID, and complete the remaining two columns on the Daily Runner Log for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the log.

Clinic staff is responsible for controlling access to the study gel cartons transferred into their custody, ensuring that the cartons are stored appropriately while in their custody, and ensuring that the cartons are delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of gel cartons to designated participants in the participants' study charts. Delivery may be documented in chart notes, on visit checklists, or on other source documents designated for this purpose by clinic staff. In the event that all gel cartons dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the remaining cartons to the pharmacy as soon as possible after the participant's visit is completed.

9.6 Return of Study Gel Supplies

Study participants will routinely return unused study gel supplies to the study site. The number of unused applicators returned at each study visit should be recorded on the Follow-up Visit form, or for interim visits, the Interim Visit form.

Participants will receive 2 cartons (20 pre-filled applicators) at the Enrollment Visit and one carton (10 applicators) at the One-Week Visit. If a participant loses or misplaces study gel after leaving the site, she will be instructed to return to the site to have new study supplies dispensed. Participants will also be given a bag containing condoms and panty liners at these visits.

ENROLLMENT VISIT

At the Enrollment Visit, site staff will instruct participants to bring all unused **wrapped** applicators, and all unused **unwrapped**, applicators that were not inserted into the vagina for any reason (i.e., fell on the floor, dropped in the toilet, etc.) to the clinic at the One-week Visit. Participants should be encouraged to keep the unused (wrapped) applicators in the carton and bring the carton with them to the clinic at the One-Week Visit. Participants are asked to return only **unused** (wrapped or unwrapped) applicators to the study clinic. Participants will be instructed to dispose of used applicators at home if possible.

ONE-WEEK VISIT

When a participant returns for the One-Week Clinic Visit, the study staff will count the unused (wrapped and unwrapped) applicators. The number of unused applicators returned should be counted and recorded on the Follow-up Visit form. The participant will keep the unused (wrapped only) applicators and bring them home after the visit for use during their second week of study participation. At the One-Week Clinic Visit, clinic staff will instruct participants to continue to use the unused, wrapped (unopened) study gel applicators in their possession first (from study gel cartons dispensed at enrollment), and then to use applicators from the new study gel supplies (dispensed at the One-Week Clinic Visit), until they come in for the Two-Week Visit. Participants will be instructed to return to the clinic for the Two-Week Clinic Visit bringing all remaining unused applicators (wrapped and unwrapped).

TWO-WEEK VISIT

When the participant returns for the Two-Week Visit, the study staff will collect all unused (wrapped and unwrapped) study product. The number of unused applicators returned should be counted and recorded on the Follow-up Visit form

All unused applicators (wrapped and unwrapped) should be stored in a biohazard container in accordance with the guidelines of the institution. The container should be a biohazard container specifically provided by the MTN for unused applicators. When the study is completed or the container is full, the biohazard container should be destroyed by autoclave in accordance with the policy of the institution.

OTHER UNUSED STUDY PRODUCT

If a participant becomes pregnant or experiences an adverse event that requires permanent discontinuation of gel use (per protocol Section 4), any unused applicators (wrapped and unwrapped) remaining in her possession should be collected from her as soon as possible and returned to the clinic on the day of collection.

It is not necessary to collect remaining applicators from participants for whom gel use is temporarily held. However, applicators may be collected from such participants, to protect their safety, if it is suspected that the participant may not comply with clinic staff instructions to refrain from gel use for the duration of the temporary hold. For all product holds requiring collection of unused applicators, if the applicators are not collected within five working days of initiating the product hold, the MTN004 PSRT must be informed, using the PSRT Query Form. When informing the PSRT, please describe the reason for the product hold, actions taken to try to collect the unused applicators, and plans and timelines for further action to collect the applicators.

If an issue or problem is identified that would necessitate collection of unused applicators from all participants, detailed instructions for collection and handling of the applicators, and documentation thereof, will be provided by the MTN Pharmacist. Other associated operational and/or data collection instructions also may be provided by the MTN CORE (FHI) and/or MTN SDMC. Clinic and pharmacy staff will follow all such instructions.

Any unused applicators remaining in a participant's possession at the time of study exit must be collected from the participant and returned to the clinic study staff on the day of collection. When planning and scheduling study exit visits, clinic staff should instruct participants to bring all remaining unused applicators to their exit visits. For participants who do not bring their remaining applicators to their exit visits, arrangements should be made to collect the applicators at the final participant contact described in protocol Section 5. For participants who do not bring their applicators to their exit visits or their final contacts, clinic staff should make all reasonable efforts to collect the remaining applicators in as timely a manner as possible, and document all such efforts in the participants' study charts. For participants for whom all reasonable efforts fail, guidance should be sought from the MTN004 PSRT.

Unused applicators collected from participants for any reason on the day of collection, should be returned to the clinic staff, clinic staff should place them in the MTN provided biohazard container. The contents of the biohazard container should be destroyed by autoclave as per site policy.

9.7 Product-Related Scenarios

For illustrative purposes, a number of product-related scenarios are provided in Section 4 of this manual (see Section Appendix 4-2b).

Section Appendix 9-1

Frequently Asked Gel Use Questions

Q1: What is the best position to insert the gel?

A: Any position that is comfortable can be used to insert the gel. The positions that are recommended are shown in the leaflet and include sitting, standing, and lying down.

Q2: What should I do if it hurts when I use the applicator to insert the gel?

A: Inserting the gel should not be painful. If you have pain when inserting the gel, try another position (sitting, standing, or lying down). If you still have pain in the new position, perhaps you need to change the angle of the applicator. The applicator should be angled slightly upward, towards your back, when you insert it. If you try to change the angle, and you still feel pain on insertion, please contact the study clinic.

Q3: Where does the gel go to after I put it inside?

A: The gel stays in the vagina until you have sex. Some gel will likely come out of the vagina during sex. The rest of the gel will come out of the vagina (through the same opening where it was inserted) over the next day after having sex. Sometimes when the gel comes out it looks clear. Sometimes it has a white color, and sometimes it has white clumps. This has been seen in other studies of the gels and it is normal. It is not normal to see a yellow or green discharge from the vagina, or a discharge with a bad odor, or with pain or itching. If this happens, it could mean you have an infection, in which case you should contact the study clinic.

Q4: Can the applicator get lost inside me?

A: No, the applicator cannot get lost inside you. When you use the applicator, hold it with your fingers about half-way along the barrel, and insert it until your fingers touch your body. Half of the barrel of the applicator should go inside your body. The other half should stay outside the body.

Q5: What should I do if I have trouble applying the gel with the applicator?

A: The applicators should be easy to use. If you have difficulty using the applicators, please contact the study clinic, as the clinic staff may be able to show you different ways that you can insert the gel, which might make it easier.

Q6: What should I do if I think there is something wrong with an applicator or its gel?

A: If an applicator does not seem to be working properly (for example, you find it difficult to push the gel out of the applicator, or if gel has leaked out, or you think there is some other problem), do not use the applicator. Use another applicator instead. Keep the applicator that had something wrong and place it in the UNUSED APPLICATOR BAG and bring it to the study staff at your next study visit. If you think that something is wrong with all of your applicators, contact the study staff as soon as possible (i.e., do not wait until your next visit) so the staff can make sure you have enough working applicators.

Q7: What happens if I press the plunger too early and most of the gel comes out on my outside?

A: If most of the gel comes out on your outside, discard that applicator and use a new applicator to insert another dose of gel.

Q8: What if I have bleeding between periods?

A: Please contact the study clinic.

Q9: How do I store the gel?

A: Store the gel in a cool, dry place.

Q10: What happens if the applicators get wet before I use them?

A: If only the wrapper gets wet, the applicator can still be used. Dry the wrapper off before taking out the applicator. If the applicator itself gets wet, it should not be used, but this might only happen if the wrapper is already open.

Q11: What should I do if the wrapper is already open when I want to use the gel?

A: You should only use applicators with sealed wrappers, so you should always open the wrapper right before inserting the gel. If you notice an applicator with a wrapper that is not sealed, do not use that applicator. Use a different applicator with a sealed wrapper instead. Keep the applicator with the open wrapper and place it in the UNUSED APPLICATOR bag and bring it to the study staff at your next study visit.

Q12: What should I do if I forget to use the gel ?

A: You should insert the gel when you remember the missed dose. If there is less than 2 hours until you will insert the next dose, that dose will be missed. Resume the schedule with the next dose. Inform the study staff of any missed doses at the next visit.

Q13: Is the gel contraceptive?

A: We don't know if the study gels will prevent pregnancy during sex acts when the gels are used. It is possible that the gels could prevent pregnancy. It also is possible they could have no effect on pregnancy (especially the placebo gel). There is no reason to think the gels will prevent pregnancy during sex acts when they are not used. If you wish to avoid pregnancy, you should use known reliable method of contraception (such as pills, injections, and condoms) while you are in this study.

Q14: Will the gel affect my partner's ability to father children?

A: No. The ingredients in the gels are not known to have any effect on male fertility. The ingredients also are not known to have any effect on female fertility.

Q15: What should I do if my partner has a reaction to the gel?

A: Contact the study clinic and ask their advice. They might ask your partner to go to the clinic to be assessed and receive treatment if needed. However, previous studies have shown this is unlikely to happen.

Q16: What should I do if I have a reaction to the gel (e.g., unusual itching, stinging)?

A: Contact the study clinic.

Q17: What should I do if I think I am pregnant?

A: Contact the study clinic immediately. The clinic staff will give you a pregnancy test to find out if you are pregnant or not.

Q18: If I use the gel, and then have oral sex, will there be a problem if my partner takes some of the gel on or in his mouth?

A: Although the safety of the study gels taken by mouth has not been studied directly, the gels are not expected to pose a safety risk if taken into the mouth or swallowed during oral sex. If at any time your

partner has a reaction to the gel, contact the study clinic and ask their advice. They might ask your partner to go to the clinic to be assessed and receive treatment if needed .

Q19: What should I do if my partner touches me in the vaginal area after the gel has been inserted? Should I re-apply the gel?

A: It is not necessary to re-apply the gel in this situation, unless you think that most of the gel has been removed. In that case, you should use another applicator to insert another dose of gel.

Q20: Does it matter what brand of condoms we use?

A: Ideally, you should use the condoms given to you by the study clinic staff. However, if you do not have one of those condoms, and you have a different condom, use that condom. Condoms are the only known way to protect against HIV and other sexually transmitted diseases (STDs), so it is always better to use any condom (even if it was not given to you by the study) than to use no condom.

Q21: Do we have to use condoms or can we rely on another form of birth control?

A: You should try to use condoms each time you have sex because condoms also protect against HIV and other sexually transmitted diseases (STDs). We do not know if the microbicide gels tested in this study protect against HIV and other STDs. Also, not all women in the study will get the microbicide gels. Some will get the placebo gel and some will get no gel. If you do not use a condom, you increase your risk of getting pregnant as well as getting HIV and other STDs. You can use another method of birth control (such as pills or injections) while in the study to give more protection against pregnancy, but you should also use condoms to protect against HIV and other STDs.

Q22: What should I do if the gel leaks out?

A: It is likely that some gel will leak out. This is normal and you don't need to do anything about it. You should always apply the full amount in the applicator. It may be helpful to wipe yourself on the outside with a dry cloth/tissue if you have been standing for a minute or two after you applied the gel, if you find that a small amount leaks out.

Q23: Can I use herbs or other substances for tight or dry sex while I am using the gel?

A: Herbs or other substances could damage the inside of the vagina. These substances also could interfere with the study gels. Therefore we recommend that you do not use herbs or other substances in the vagina.

Q24: Can my partner insert the gel for me?

A: It is preferable that you insert the gel yourself, but if you are happy that your partner knows how to do it in a way that won't cause you discomfort, then this is acceptable. It is better for your partner to insert the gel for you than to not use the gel at all.

Q25: Will I have access to the gel if it is shown to be effective?

A: If the gel is shown to be safe and effective, it will take some time for the gel to be allowed to be sold in the shops, but we will try to make sure this happens as quickly as possible.

Q26: My sister and I are both in the study and we live in the same house. What should we do if we mix up our gel?

A: First, try not to mix up your gel. If possible, keep the applicators in the cartons, and check for your study number on the carton to help make sure you each use the gel that you received. We also can give you some

colored stickers (or other identifiers if applicable) to put on your cartons and applicators to help keep track of whose gel is whose.

If you do mix up your applicators, the most important thing for you to do is inform the study staff, so we can have the pharmacist help you sort out whose gel is whose. It is okay to report mix-ups to us. We know that mix-ups can happen, and you will not be penalized if you mix up your applicators. You can still be in the study, and keep using gel, so long as you are willing to try to avoid more mix-ups. Please tell us as soon as possible if any mix-ups occur.

Section Appendix 9-2

MTN 004 Record of Receipt of Participant-Specific Gel Cartons

Site Name:
Site Number:

Clinic Name:

PHARMACY STAFF				CLINIC STAFF			COMMENTS
Date Dispensed by Pharmacy dd-MMM-yy	*PTID	No. of Study gel cartons Dispensed by Pharmacy	Pharmacist Initials	PTID <i>*(Verify PTID transcribed from box matches PTID recorded by Pharmacist in Pharmacy Staff Section)</i>	Date and Time Received in Clinic (dd MMM yy, 00:00 AM/PM)	Clinic Staff Initials	

Instructions: Complete one row each time participant-specific study gel cartons are dispensed to non-pharmacy staff for delivery to a study participant. All entries must be made in dark ink. Corrections may be made by drawing a single line through incorrect entries, entering correct information, and initialing and dating the correction.

*** Form must be returned to the pharmacy at the end of every business day**

Section Appendix 9-3

MTN 004 Daily Runner Log

Site Name:
Site Number:

Clinic Name:

PHARMACY STAFF				RUNNER			COMMENTS
Date Dispensed by Pharmacy dd-MMM-yy	*PTID	No. of Study gel cartons Dispensed by Pharmacy	Pharmacist Initials	PTID <i>*(Verify PTID transcribed from box matches PTID recorded by Pharmacist in Pharmacy Staff Section)</i>	Date and Time Received by Clinic Staff (dd mmm yy, 00:00 AM/PM)	Runner Initials	

Instructions: Complete one row each time participant-specific study gel cartons are dispensed to non-pharmacy staff for delivery to a study participant. All entries must be made in dark ink. Corrections may be made by drawing a single line through incorrect entries, entering correct information, and initialing and dating the correction.

*** Form must be returned to the pharmacy at the end of every business day**

Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in MTN 004. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 12. Instructions for completing data collection forms associated with clinical procedures are provided in Section 14.

10.1 Baseline Medical/Menstrual/Genitourinary History and Ascertainment of Concomitant Medications

A focused baseline medical/menstrual/genitourinary history is obtained from potential study participants at the Screening 1, Screening 2, and Enrollment Visits. Medications used by the participant also are ascertained and documented at this time. The purpose for obtaining this information during screening is to:

- Assess and document participant eligibility for the study at the Screening and Enrollment visits
- Assess and document the participants' baseline medical conditions and symptoms and symptoms, for comparison with signs, symptoms, and conditions that may be identified or reported during follow-up
- Monitor any potential AEs associated with the use of the gel during the course of the study

10.1.1 Focused Baseline Medical/Menstrual/Genitourinary/Genitourinary History

The non-DataFax Baseline Medical History form is a recommended source document for collecting pertinent baseline medical/menstrual history data. Alternative site-specific history forms also may be used. For enrolled participants, all baseline conditions identified as ongoing at the time of the Enrollment Visit are documented on the (DataFax) Pre-existing Conditions form. Recurring and/or chronic conditions are considered ongoing whether or not they are present/active at baseline.

The non-DataFax History of Genital Symptoms form is the recommended source document for collecting data on genitourinary symptoms, including intermenstrual bleeding/spotting, that the participant has experienced from the time she became sexually active through her last Screening Visit. The Baseline Genital Symptoms form is the source document for collecting data on genitourinary symptoms that the participant experienced from the time of her last Screening Visit through Enrollment.

When obtaining a focused baseline medical/menstrual history and completing the History of Genital Symptoms form for MTN 004, it is not necessary to document the participant's lifetime medical history and/or history of genitourinary symptoms. Rather, focus on conditions that have occurred and symptoms that were experienced since the participant became sexually active, and probe for the most accurate information available on the participant's current health and reproductive status vis-à-vis the reported history. Several additional guidelines are presented below:

- Use the listing of body systems on the Baseline Medical History form to probe for history related to each system.
- Record symptoms, illnesses, allergies, and surgeries.
- Record both chronic and acute conditions, as well as both ongoing and resolved conditions.
- For menstrual history, document the details of the participant’s usual menstrual cycle and flow. Also enter the first and last day of the participant’s last menstrual period, and the average number of bleeding days (e.g., 3-5 days) she experiences during her regular menses. Note the participant’s age of menarche and any menstrual problems she may have, such as irregular menses, amenorrhea, menorrhagia, etc. Document the type and severity of any usual menstrual symptoms.
- Document any usual or typical non-menstrual genital bleeding patterns experienced by the participant. This includes any breakthrough genital bleeding/spotting associated with the participant’s contraceptive use. Include the frequency of bleeding, the average duration, type of flow (e.g. light, moderate, heavy) and any associated symptoms.
- For all genitourinary subcategories listed on the History of Genital Symptoms and Baseline Genital Symptoms form, probe for and record as much detail as possible. Detailed baseline information in these categories is critical, since changes from baseline will be considered adverse events (AEs; see Section 11). As part of the “other” genitourinary subcategory, explore whether the participant experiences bleeding during or after vaginal intercourse and whether she has experienced (or continues to experience) any type of sexual trauma.
- For reproductive history, record the number, date, and outcome of each of the participant’s pregnancies, as well as any gynecologic and obstetrical procedures/surgeries.
- Record the participant’s history of contraceptive use. If applicable, enter details of the participant’s current contraceptive method on the Concomitant Medications Log form. Per Section 5 of the study protocol, spermicides, diaphragms, and contraceptive vaginal rings should not be used during participation in MTN 004. Participants who report current use of these contraceptive products and devices during screening must be counseled regarding the use of alternative methods and should be referred to family planning services if needed for provision of alternative methods prior to enrollment in the study.
- Document medications currently taken for all ongoing conditions, including usual menstrual symptoms, on the Concomitant Medications Log form, as described in Section 10.1.2.

Site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in English (and Spanish for the San Juan, PR site) to elicit complete and accurate history information from study participants.

10.1.2 Initial Ascertainment of Concomitant Medications

The MTN 004 protocol requires documentation of all medications taken by study participants beginning at the Screening 1 Visit and continuing throughout follow-up. For purposes of this study, medications include all of the following, regardless of route of administration:

- Prescription and “over-the counter” medications and preparations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Recreational drugs

Other routes of administration, including intravaginal and rectal medications/preparations and topical medications/preparations applied to the external genitalia are of particular interest for this study, as are douches and vaginal cleansers. Be sure to record all such medications/preparations.

The Concomitant Medications Log form is the recommended source document for collecting information on participants’ use of medications. When recording the route of medications/preparations that are applied intravaginally, mark the box labeled “VAG”. When recording the route of medications/preparations that are applied rectally, mark the box “REC.”

It is recommended that study clinicians ascertain participants’ baseline medication information in the context of conducting the baseline medical/menstrual history. In addition to asking open-ended questions to elicit participant report of current medications, use the information obtained in the medical/menstrual history to probe for additional medications that the participant may forget to report. For example, if the participant reports recurrent headaches as part of her medical history, but does not spontaneously list any medications taken for headaches, ask her if she takes any medications for the headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the Baseline Medical History form and Pre-existing Conditions form as appropriate.

10.1.3 Pre-existing Conditions

As noted above, a key purpose of conducting the baseline medical/menstrual history — as well as the abdominal exam and Screening 1 pelvic exam described below — is to document participants’ baseline medical conditions, for comparison with signs, symptoms, and conditions that may be identified or reported at subsequent scheduled or interval study visits. For MTN 004, all ongoing medical conditions, problems, signs, symptoms, and (abnormal) findings that are observed and/or reported *at enrollment* are considered pre-existing conditions. Such conditions should be documented per the screening and enrollment visit guidance provided in Sections 4 and 7 of this manual, as well as in the remainder of this section.

For participants who enroll in the study, all conditions observed and/or reported at the Enrollment Visit should be reported on the Pre-existing Conditions form. This case report form is completed at the Enrollment Visit, based on all other screening and enrollment source documents, including the Baseline Medical History form, Physical Exam form, Screening 1 Pelvic Exam form, all screening laboratory results, chart notes, and any other site-specific source documents.

As is described in greater detail in Section 11, the Pre-existing Conditions form serves as the “starting point” from which study clinicians must determine whether medical conditions, problems, signs, symptoms, and other abnormal findings identified or reported during follow-up are adverse events (AEs). By definition, pre-existing conditions are present at the time of randomization/enrollment in the study and are therefore are not considered AEs. However, new conditions identified during follow-up that were not present at the time of enrollment/randomization, and any pre-existing conditions that increase in severity or frequency during follow-up, are considered AEs. With this in mind, when completing the source documents listed above, as well as the Pre-existing Conditions form, study clinicians should document as much detail as possible about the severity and frequency of each pre-existing condition. When completing the Pre-existing Conditions case report form, it is recommended that this information be recorded in the “Comments” section for each condition.

10.2 Interval Medical/Menstrual/Genitourinary History and Updating of Concomitant Medications

For enrolled participants, an interval medical/menstrual/genitourinary history and update of concomitant medications is obtained at each scheduled follow-up visit. This procedure also is performed at interim visits when clinically indicated. An interval medical/menstrual/genitourinary history is considered clinically indicated at interim visits if the participant presents for the interim visit complaining of any symptoms since the last visit. The purpose of these procedures is to determine whether participants have experienced any new illnesses, symptoms, etc., since the last study visit. An interval medical/menstrual/genitourinary history also should be performed at interim visits to obtain updated information on previously reported adverse events when applicable.

10.2.1 Interval Medical/Menstrual/Genitourinary History

The non-DataFax Follow-up Medical History Form is a recommended source document for collecting interval medical/menstrual history data.

At the first One-Week Clinic Visit (day 6-8), retrieve the participant’s non-DataFax Baseline Medical History and Pre-existing Conditions forms for reference. At the Two- and Three-Week Clinic Visits, retrieve the participant’s Follow-up Medical History (non-DataFax) form from the prior visit for reference. When completing each interval history, it is not necessary to actively review/inquire about every body system listed on the Follow-up Medical History Form. Rather, for all systems except genitourinary, it is acceptable to actively inquire about the current status of conditions recorded as ongoing at the time of the prior visit, and then to ask the participant an open-ended question such as “Have you had any other symptoms or health problems since your last visit?” to complete the history. The Follow-up Genital Symptoms form is a source document used to document genitourinary symptoms experienced during follow-up. Unlike the Follow-up Medical History form, DO NOT refer to any previously completed genital symptoms forms (i.e., History of Genital Symptoms, Baseline Genital Symptoms, Follow-up Genital Symptoms) when completing the Follow-up Genital Symptoms form for the current visit. Rather, for each genital symptom listed on the form, actively inquire as to whether the participant experienced the symptom since her last study visit.

See Section 10.6 below for more information on assessing participant reports of genital bleeding.

Site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in English (or Spanish for the San Juan, PR site) to elicit complete and accurate follow-up information from study participants.

10.2.2 Updating of Concomitant Medications Information

At each visit in which an interval medical/menstrual history is obtained, retrieve the participant's Concomitant Medications Log, record any new medications taken by the participant, and actively inquire as to whether the participant is still taking medications listed previously, at the same dose and frequency. Also actively inquire as to whether the participant has begun taking any new medications since her last visit, including medications obtained outside the study (not provided by the study staff). To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc., since her last visit, inquire as to whether she took any medications for these. Add all new information to the form in log fashion, using additional form pages as needed. Similarly, if a participant reports taking a new medication for a condition that she inadvertently did not report when providing interval medical/menstrual history information, add the condition to the Follow-up Medical History form, and Pre-existing Conditions form (if present at enrollment).

10.3 Behavioral Measures

Each study site will have a computer terminal connected to the Web that the participants will use three times during the study to respond to Behavioral Measures. This computer terminal will be placed in such way to assure the confidentiality of the participants' responses (i.e. the screen will be out of site of staff members or other participants while answers are being entered). Behavioral Measures are:

- Baseline Behavioral Questionnaire, taken at the Enrollment Visit,
- Acceptability and Adherence Questionnaire, taken at the Two-Week Clinic visit,
- Study Burden Questionnaire taken at the Three-Week Clinic Visit

Note: It is recognized that study clinicians will be unable to review participants' responses to the behavioral measures (BM) prior to conducting interval medical/menstrual histories. It also is acknowledged that detailed clinical probing of responses may identify discrepancies between the BM data and the history information recorded by the clinician. In the event that discrepancies occur, information recorded by the clinician will be considered primary for purposes of monitoring participants' clinical condition and documenting clinical study endpoints. To preserve the standardization of behavioral data collection, however, BM responses will not be amended to correspond with the information recorded by the clinician.

10.4 Physical Exams

An assessment of vital signs and an abdominal exam are required at the Screening 1, Enrollment, One-Week, Two-Week, and Three-Week Clinic Visits. Site clinicians may use their discretion to determine whether or not to conduct a more complete physical exam, in response to reported symptoms or illnesses present at the time of the exam. Following is a list of the required vital sign assessments, as well as a list of clinical assessments.

Vital signs:

- Weight
- Height
- Oral temperature
- Blood pressure
- Pulse
- Respirations

Clinical assessments of:

- Head and eyes (HE)
- Ears, nose, and throat (ENT)
- Neck
- Lymph nodes
- Heart
- Lungs
- Abdomen
- Extremities
- Neurological
- Skin
- Breasts

The non-DataFax Physical Exam form is a recommended source document for recording physical exam findings. For participants who enroll in the study, abnormal physical exam findings identified at the Enrollment Visit also are recorded on the Pre-existing Conditions form.

Physical exams may identify additional baseline medical history information that participants inadvertently do not report in their baseline medical/menstrual history. For example, the clinician may identify a skin condition during the physical exam and upon further inquiry learn that the participant has had the condition since age 15. In such situations, the clinician should add the newly identified information to the non-DataFax Baseline Medical History form, and the Pre-existing Conditions form as well, since the condition was present at the time of enrollment.

10.5 Pelvic/Colposcopic Exams

Pelvic exams are performed in MTN 004 for purposes of determining eligibility and identifying primary study safety outcomes. As such, they are critical to meeting the study objectives and ensuring the ongoing safety of study participants. Pelvic exams are performed at Screening 1 Visit and all study visits thereafter per the schedule in protocol Section 7. Exams also are performed when clinically indicated to evaluate genital symptoms.

Colposcopy is required at the Enrollment and Two-Week Clinic Visits. If clinically indicated, colposcopies may be performed at the One-Week and Three-Week Clinic Visits as well.

Pelvic/colposcopic exams are performed, and findings classified, according to the CONRAD/World Health Organization (WHO) Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004 (available at www.conrad.org), and the remainder of this section. Exam procedures must be performed in the order shown on the exam checklists in Section 7 of this manual. All procedures listed on the exam checklists should be performed during routinely scheduled exams. When additional exams are performed to assess genital symptoms, only clinically indicated procedures should be performed. As indicated in greater detail below, exam findings are reported on the following forms provided by the MTN SDMC:

- Screening 1 and Enrollment Pelvic Exam (SPE-1-2)
- Screening 2 Pelvic Exam (RSP-1)
- Follow-up Pelvic Exam (FPE-1-3)
- Pelvic Exam Diagrams (non Datafax form)
- Pelvic Laboratory Results (PLR-1)

For participants who enroll in the study, abnormal exam findings identified at the Enrollment Visit (that are not exclusionary per the study eligibility criteria) also are recorded on the Pre-existing Conditions form.

10.5.1 Overview

General Technique: Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to assure participant comfort and accurate documentation of exam findings.

Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed to adjust equipment.

Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix. For most participants, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. Prior to insertion, ensure that the speculum functions properly and has no rough edges. The speculum may be lubricated with warm water if needed. No other lubricant may be used.

Record the length and axis of the vagina, position of the cervix, and type and size of speculum after each participant's first examination (e.g., on the exam checklist or Pelvic Exam Diagrams form). This information can then be reviewed prior to subsequent exams to reduce the risk of iatrogenic injury.

Lavage and Removal of Visual Obstruction: During the exam, after assessment of vaginal pH and collection of vaginal swabs, if necessary remove any obstruction (e.g., mucus, cellular debris) by lavage with sterile, isotonic, non-bacteriostatic saline. Avoid contact between the pipette and the epithelium. The lateral fornices may be lavaged without manipulation by directing the stream into them. Aspirate the fluid with the tip of the pipette against the inner surface of the posterior blade of the speculum. Do not lavage prior to assessing pH and collecting swabs for wet prep, Gram Stain, cytokines and innate factors testing, quantitative vaginal culture, and GUD testing, per study visit requirements.

If lavage does not adequately remove the obstruction, use a large saline-moistened swab (scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium.

Specimen Collection: Perform specimen collection during each exam in the sequence specified on the pelvic exam checklists (see Section 7 of this manual).

Use of Magnification: For each area examined, i.e., the external genitalia, cervix, and vagina, first perform naked eye exam. Then proceed to colposcopic exam using low power (x4-10 magnification) and no filter to more closely examine the tissues. Colposcopic examination of the external genitalia must precede insertion of the speculum.

Documentation of Findings: Document all exam findings — both normal and abnormal — on the Pelvic Exam Diagrams form. Document abnormal findings only on the appropriate pelvic exam form case report form. Both the Screening Pelvic Exam form and the Follow-up Pelvic Exam forms are recommended source documents for recording relevant descriptors and details of abnormal findings. However, supplemental information may be recorded on the Pelvic Exam Diagrams form, in chart notes, and/or on other source documents. For participants who enroll in the study, abnormal exam findings identified at the Screening 1 Visit (that are not exclusionary per the study eligibility criteria) also are recorded on the Pre-existing Conditions form. See Section 10.5.3 for detailed instructions on classifying and documenting exam findings.

Imaging: Records of digital colposcopic images are required for enrollment and for any findings at follow up visit examinations. The colposcopist will document findings in the participant's chart notes and on the study case report forms. When there are findings on the follow up visits, the clinician should retain digital video images in order to complement documentation of baseline findings, abnormal findings or injury. Save images before probing or swabbing any findings. The informed consent document will include consent to obtain these digital images.

Organizing Colposcopy Images: A large number of colposcopic images will be obtained at each study site. The following naming and filing procedures will ensure consistent organization across sites and facilitate review of images.

Folders for each Subject:

Each subject will have her own dedicated file in which all that participant's saved colposcopic images will be stored. The following format should be used to name the subject's main study folder: Site_PTID

Example: Tampa_300123456

Folders for each Visit:

Within each subject's main study folder there will be subfolders for different visits. The following format should be used to name the subject's subfolder:

Site_PTID_datecollected_colposcopist's initials

Example: PR_301123456_29Oct08_MC

Library for each Visit, if needed for image capture software:

The Library should be named using the following format:

Site_PTID_datecollected_colposcopist's initials

Example: Pitt_302123456_29Oct08_MC

Videos of images:

Videos and images will be saved using the following format:

Site_PTID_datecollected_anatomiclocation_#

Examples: PR_301123456_29Oct08_cervix_1

Uploading Colposcopy Images:

Each study site is asked to upload all colposcopy images and videos collected for the first five participants enrolled under protocol version 3.0. Sites should upload all images and videos collected for each participant, starting with images/videos from the Enrollment Visit.

Sites should be certain to collect and upload at least one image each from the following anatomical locations: vulva, cervix, fornix-right, fornix-left, fornix-anterior, and fornix-posterior. All videos/images should be uploaded within 2 business days of the visit.

When you are ready to upload an image or video files:

1. To upload colposcopy image/video files, you will need:
 - a) The image and video files available on the computer to access the Atlas web portal
 - b) You will need to know the PTID, Visit Code, and Date of Procedure (Exam Date) for each set of participant files you wish to upload.
 - c) You will need to have already renamed each image and video file you plan to upload, and will need to know the location of the files on the computer, using the following convention:

Site_PTID_datecollected_anatomiclocation_#

For example, an image file from the Tampa site collected for PTID 300-12345-6 on 29-Oct-2008 would be named "Tampa_300123456_29Oct08_cervix_1". If a second image was taken on this same day for the same PTID and location, it would be named "Tampa_300123456_29Oct08_cervix_2". For the San Juan, Puerto Rico site, use "PR" for the site in the filename (ex. PR_301123456_29Oct08_cervix_1). For the Pittsburgh site, use "Pitt" for the site in the filename (ex. Pitt_302123456_29Oct08_cervix_1)

Note: Files for upload must not exceed 250 MB and ALL files must be named uniquely.

2. Go to the MTN 004 Atlas web page by accessing this link: <https://atlas.ssharp.org/cpas/project/MTN/004/begin.view>, or, in your web browser, type in “atlas.ssharp.org”, click on the “MTN” button, and then click on “MTN 004.”
3. Make sure you are signed in to Atlas – in the upper right-hand corner of the screen, click on “Sign in”. Enter your full email address along with your Atlas password. If you have any problems signing in, email atlas@sharp.org.
4. On the MTN 004 Atlas web page, in the paragraph under the “004 Colposcopy Images and Videos” heading, click on the “Colposcopy Image and Video Upload Screen” text
5. You should now be on the page titled “Colposcopy Image and Video Upload Screen”. Complete the “Participant Information” fields - Participant ID (PTID), Visit Code, and Date of Procedure. If you are unsure about how to complete these items, see the examples listed and/or place your mouse over the “?” present to the immediate left of each data field for additional information
6. Upload up to two video files and up to 10 photo files using the “Browse” buttons to search for files on your computer or network.
7. Once you have browsed and selected all of the image and video files you wish to upload for the participant, enter any relevant comments in the text box provided. Once you are ready to have the files upload, click the “Submit” button at the bottom of the page. Remember that files will not be uploaded until you have submitted the form by clicking the “Submit” button.
8. Once the “Submit” button has been clicked, a confirmation page will appear, indicating that all fields have been correctly completed on the upload screen. If you have any questions or problems uploading files, please email atlas.ssharp.org

10.5.2 Detailed Procedural Instructions

Study-specific pelvic exams should not be performed during menses, since the presence of menstrual blood will likely interfere with visualization of the vagina and cervix, elevate the vaginal pH, and complicate interpretation of wet prep findings. If a participant is menstruating when she presents for a visit in which a pelvic/colposcopy exam is required, perform other protocol-specified procedures at the visit and schedule the participant to return for the pelvic exam and associated specimen collections as soon as possible after menses, within the allowable visit window. If a participant is menstruating when she presents for an interim visit complaining of genital symptoms, every effort should be made to perform a pelvic exam to evaluate her symptoms at that time. However, if this is not possible the participant should be instructed to return for a pelvic exam as soon as possible after menses.

See Section 6 of this manual for procedural modifications to be followed with pregnant participants.

Prior to the Exam: Prepare all required equipment, supplies, and paperwork. Verify that all equipment is in good working order and that the colposcope, computer, software, and printer are warmed up and ready for use (for exams involving colposcopy). Review documentation of prior exams (if any) and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure and equipment to her and answer any questions she may have.

Position the Participant: Establish a comfortable examination position for the participant that allows for the perineum and vulva to be inspected. Adjust stirrups and back elevation as needed. Provide socks if the room is cold; provide a fan for the participant's face if the room is warm. Drape the participant and point out distractions such as photos on the ceiling or music if available.

Examine the External Genitalia:

- Do not insert the speculum prior to examining the external genitalia.
- Spread the participant's knees as far apart as is comfortable for her.
- Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness.
- Perform naked eye examination of the external genitalia including the perineum, perianal area, and the epithelial lining of the introitus.
- For exams involving colposcopy, proceed to colposcopic examination of the same areas, using appropriate magnification.
- Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the appropriate pelvic exam case report form.

Examine the Cervix:

- The speculum may be lubricated with warm water if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles, using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina.
- If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum.
- Perform naked eye exam without manipulation, observing the general state of the cervix, the size and shape of the cervical os, and any other findings.
- During exams not involving colposcopy, assess cervical ectopy at this time. During exams involving colposcopy, assess cervical ectopy during the colposcopic exam.
- Assess for homogeneous discharge. Record outcome on the Pelvic Laboratory Results form. If any abnormal vaginal or cervical discharge and/or blood-tinged discharge are also present, document the discharge on the Pelvic Exam Diagrams and on the appropriate pelvic exam form (Screening 1 and Enrollment Pelvic Exam form, Screening 2 Pelvic Exam form, or the Follow-up Pelvic Exam form).
- Place pH indicator strip against lateral vaginal wall, just until the paper is moistened. Avoid contact with cervical mucus, which has a high pH. Alternatively, vaginal fluids may be collected via swab and then swabbed onto the pH strip (instead of inserting the pH strip into the vagina). Match the resulting color of the pH strip to the color scale provided with the strips to determine the pH value. Record the pH on the Pelvic Laboratory Results form.

- Collect vaginal fluids via (dry) swab for wet prep, Gram Stain, and quantitative culture, as required by the visit. Collect fluids from the lateral vaginal wall, away from any apparent abnormalities. Collect cervical fluids (dry) swab for cytokines and innate factors testing. Collect fluids from the cervical canal, away from any apparent abnormalities. Exclude swabbed areas from subsequent examination. Document specimen collection for Gram Stain on the Screening Pelvic Exam form or the Follow-up Pelvic Exam form. See Section 12 of this manual for detailed wet prep and Gram Stain slide preparation and assessment procedures.

Wet prep slides are to be read by local laboratory or site research staff, and results should be recorded on the Pelvic Laboratory Results form. Gram stains are to be read at the MTN Network Laboratory (NL), so results will be forwarded directly to SCHARP by the NL.

- If needed, lavage the cervix and vagina as described in Section 10.5.1 and complete naked eye exam.
- For exams involving colposcopy, proceed with colposcopic examination of the cervix, fornices (anterior, right lateral, left lateral, and posterior), and adjacent cervical trunk using appropriate magnification (usually 4-10X). If excessive glare occurs, reposition to alter the illumination angle. If necessary, manipulate the speculum slightly so the fornices may be adequately visualized. The lateral fornices are best exposed by placing a saline-moistened large swab (scopette) into the contralateral fornix and pressing toward the participant's head and laterally. For example, to view the right lateral fornix, place the moistened swab into the left lateral fornix and press gently toward the participant's head and left side. Do not use dry swabs for this purpose.
- Note all findings (variants of normal and abnormal) on the non-DataFax Pelvic Exam Diagrams form. See the variants of normal in section 10.5.3 below. Further document abnormal findings on the appropriate pelvic exam case report form. Save images of abnormal colposcopic findings per Section 10.4.1.

Examine the Vagina: To examine the rest of the vagina, slowly withdraw the speculum with the blades moderately open, re-focusing as needed. Alternatively, the speculum may be rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate. Note all findings on the Pelvic Exam Diagrams form. Further document abnormal findings on the appropriate pelvic exam case report form.

Collect Genital Ulcer Swabs: If any genital ulcers are observed during follow-up, swab the base of the ulcer using a dry plastic shaft Dacron swab. Use a different swab for each ulcer. If a cluster of ulcers is observed, sample each ulcer in the cluster with the same swab. Otherwise use a different swab for each ulcer. Document specimen collection on the Follow-up Pelvic Exam form. See Section 12 of this manual for further instructions for proper swab handling and storage prior to testing at the MTN Network Laboratory.

Collect Pap Smear: A Pap smear is required at the Screening 1 Visit if there is no documentation of a normal result in the form of a written report within the 12 calendar months prior to screening. If no such documentation exists, collect ecto- and endocervical cytobrush specimens after completing all naked eye and colposcopic tissue examinations. Document specimen collection on the Pelvic Laboratory Results form and transcribe results, once they become available, to that same form. Participants with abnormal results will not be eligible for the study. Pap smears will be reported as per the 2001 Bethesda System and will be presumed normal in the absence of intra-epithelial lesion or malignancy.

Perform Bimanual Exam: After completing all tissue examinations and specimen collection, close the speculum blades, gently remove the speculum, and perform bimanual exam for adnexal or fundal masses and/or tenderness.

10.5.3 Documentation of Findings

Document all exam findings, both variants of normal and abnormal, on the Pelvic Exam Diagrams form.

The following findings are considered normal:

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner's duct cysts
- atrophic changes
- blood vessel changes other than disruption
- skin tags
- scars

Per the CONRAD/WHO Manual, abnormal findings will be classified according to the state of the epithelium and blood vessels associated with the finding, as follows:

Epithelium

Integrity:

- Intact
- Disrupted:
 - Superficial
 - Deep (complete disruption is considered deep and exposes stroma and possibly blood vessels; a bleeding area is considered deep)

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes "pale")

Blood Vessels

Integrity:

- Intact
- Disrupted

Figure 10-1 provides information to guide and standardize terminology used to describe abnormal pelvic exam findings. Examining clinicians also are encouraged to consult the Photo Atlas for Microbicide Evaluation developed by Bollen, Kilmarx, and Wiwatwongwana (MOPH-US CDC Collaboration, 2002) for further examples of terminology applied to pelvic exam findings in microbicide studies.

The Screening 1 and Enrollment Pelvic Exam form, the Screening 2 Pelvic Exam form (if applicable), and the Follow-up Pelvic Exam form are recommended source documents for recording relevant descriptors and details of abnormal findings; however supplemental information may be recorded on the Pelvic Exam Diagrams form, in chart notes, and/or on other source documents. Iatrogenic findings such as those caused by speculum trauma should be included among the “abnormal” findings documented for the exam, with notations added to source documents and case report forms to specify the cause of the finding.

10.5.4 Quality Control

A quality control measure will be implemented to ensure that sites are recording colposcopic findings consistently. All digital images obtained from the first five participants enrolled at each site after study resumption will be sent to the University of Pittsburgh colposcopy consultants for review. Should there be discrepancies in reporting between sites and/or participants, additional colposcopic training can be arranged.

Figure 10-1
CONRAD/WHO Terminology for Pelvic Exam Findings

Term	Status of Epithelium	Status of Blood Vessels	Comments	
Erythema	Intact	Intact	Distinguished by color (erythema being redder than normal, edema either normal or paler than normal, and grossly white findings being white). Grossly white findings are sharply demarcated whereas edema and erythema may be sharp or diffuse.	
Edema	Intact	Intact		
Grossly white finding	Intact	Intact		
Petechiae	Intact	Disrupted	≤ 3 mm	Color of finding is red or purple.
Ecchymosis	Intact	Disrupted	> 3 mm	
Peeling	Disrupted, superficial	Intact	Fragment of disrupted epithelium may remain attached to the area from which it has peeled off. Generally has well demarcated outline. Underlying epithelium looks normal	
Ulcer	Disrupted, superficial or deep	Intact or disrupted	May include sloughing at base. Generally round or oval with sharply demarcated outline. Superficial ulcers are more accurately called erosions.	
Abrasion	Disrupted, superficial or deep	Intact or disrupted	Distinguished from other findings in this class by diffuse or poorly demarcated outline.	
Laceration	Disrupted, superficial or deep	Intact or disrupted	Sharply demarcated linear finding. Includes fissures. Lacerations appear to be the result of trauma. Fissures appear to be linear “pulling apart” or wearing away of tissue.	

Note: Superficial epithelial disruption does not penetrate into subepithelial tissue. Deep epithelial disruption penetrates into and exposes the subepithelial tissue and possibly blood vessels. If bleeding from the finding is present, the disruption is considered deep.

10.6 Genital Bleeding Assessment

Genital bleeding other than menstrual bleeding, often referred to as “intermenstrual bleeding” or “IMB” is a common occurrence among reproductive age women, and often is of physiologic or benign etiology. Some women normally experience mid-cycle bleeding or pre-menstrual bleeding. IMB is common in oral contraceptive users, particularly new and/or inconsistent users. Use of intrauterine contraceptive devices, smoking, and chlamydia infection have been identified as risk factors for IMB, and IMB may be associated with genital tract pathology such as cancer or polyps. IMB also may be associated with traumatic injury to the cervicovaginal epithelium (e.g., due to speculum insertion, product applicator insertion, sexual activity).

Background rates of IMB in the general population are not known with precision. In a recent survey of HIV-negative and HIV-positive women, 12 percent and 11 percent respectively reported IMB in the last six months. In clinical trials of oral contraceptives, IMB rates have ranged from five percent to over 50 percent. The high variability in IMB rates seen in these studies is likely due to different methods of data collection and reporting as well as cultural factors. Regardless, since oral contraceptive trials generally are not placebo controlled, it is difficult to assess how rates reported in those trials compare to background rates in the general population.

Similar to observations in contraceptive trials, variable rates of IMB have been observed in Phase I microbicide trials, many of which have not included a control group. While IMB has been reported in microbicide trials, IMB has not been associated with anemia or hemodynamic instability in those trials. The main concern raised by observation of IMB in microbicide trials is that candidate microbicides that are associated with increased rates of IMB may increase, rather than decrease, the user’s risk of HIV infection, presumably by disrupting the cervicovaginal epithelium and blood vessels. Increased rates of IMB also might affect the microbicide’s acceptability.

The MTN 004 Protocol Team has carefully considered the potential risks that may be associated with IMB and has developed procedures to evaluate, monitor, and report on genital bleeding throughout the course of the study. These procedures are described below and several possible genital bleeding assessment scenarios are presented in Appendix 10-1.

10.6.1 Genital Bleeding Assessment for Pregnant Participants

The remainder of this section provides procedural instructions and guidance for assessment of genital bleeding among non-pregnant participants. If a pregnant participant reports genital bleeding, study staff will clinically manage the participant per local practice standards for pregnancy. In particular, study staff will refer the participant to a qualified clinician for further evaluation, care, and treatment; pelvic exams may be performed by qualified clinicians unless contraindicated. Study staff will document the bleeding event and all follow-up actions in the participant's study records. When reporting the event as an AE, it is not expected that a term such as "intermenstrual bleeding" or "metrorrhagia" will be used to describe the AE. Rather clinically appropriate terminology reflecting the cause or source of the bleeding (e.g., "threatened abortion") should be used, if possible, and the bleeding itself should be graded according to the "First trimester bleeding", "Second/third trimester bleeding", or "Postpartum hemorrhage" row of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 December 2004, Addendum 1 (The Female Genital Grading Table for Use in Microbicide Studies) as appropriate. Any questions related to genital bleeding assessment or AE reporting for pregnant participants should be submitted to the MTN 004 PSRT as described in Section 11.

10.6.2 Participant Reports of Genital Bleeding

As part of the MTN 004 informed consent and enrollment process, study participants will be counseled to report all occurrences of genital bleeding — other than usual menstrual bleeding — to the study site as soon as possible after identification of the bleeding. Study staff will provide site contact information to each participant upon enrollment. Thereafter, at each study follow-up visit, contact information will be reiterated and active reporting of genital symptoms including unexpected menstrual bleeding and unexpected non-menstrual genital bleeding will be emphasized.

As described in Section 10.2, at each study visit, clinicians will obtain interval medical/menstrual history information from participants, including active ascertainment of whether any genitourinary symptoms including genital bleeding were experienced since the last study visit. Any changes in participants' use of concomitant medications, including contraceptives and topical and intravaginal medications/preparations, also will be actively ascertained. Reports of genital bleeding should be recorded on the Baseline Genital Symptoms form (at enrollment) or on the Follow-up Genital Symptoms form (for follow-up visits).

10.6.3 Clinician Assessment of Genital Bleeding

Study participants will undergo pelvic exams at the Screening 1 Visit, Enrollment and at every weekly visit thereafter. Pelvic exams also will be performed to evaluate any participant report of unexpected menstrual bleeding and/or unexpected non-menstrual genital bleeding. Pelvic examinations will be performed and documented as described in Section 10.5.

Figures 10-2a and 10-2b outline the genital bleeding assessment and reporting procedures that will be followed at all sites. As shown in the figures, the sequence of procedures will differ depending on whether genital bleeding is first reported by the participant or first observed on pelvic exam. The Genital Bleeding Assessment form (see Section 14) will be used at all sites to guide and document clinicians' assessment of both participant-reported genital bleeding and clinician-observed genital bleeding when applicable (see more below). The Genital Bleeding Assessment form guides clinicians to collect and consider information on the many factors that may contribute to the observation of genital bleeding, to help determine whether the bleeding may be related to product use, or whether it may be more likely attributable to another cause. These factors include:

- Early onset of menses
- Use of hormonal contraceptive methods
- Use of intrauterine contraceptive devices
- Missed oral contraceptive pills or injections
- Sexual activity/trauma
- Trauma associated with insertion of study product or other vaginal preparations
- Trauma associated with pelvic exam procedures
- Sexually transmitted or reproductive tract infections/outbreaks
- Epithelial and/or blood vessel disruption observed on pelvic exam
- Other pathology observed on pelvic exam (e.g., polyps, carcinoma)

Assessment of genital bleeding should begin by determining whether the bleeding is *expected* or *unexpected*, and then proceed to determining whether the bleeding is *menstrual* or *non-menstrual*. Expectedness will be determined based on the participant's baseline medical/menstrual history (e.g., whether she reports genital bleeding as a pre-existing condition) as well as any other relevant factors such as hormonal contraceptive use. If a participant reports bleeding consistent in amount and duration with her baseline menstrual history, or that is consistent with use of her hormonal contraceptive method, the bleeding will be considered *expected*. In particular, intermenstrual genital bleeding occurring within the first three months of initiating a hormonal contraceptive method will be considered expected, unless the study clinician determines that the bleeding is inconsistent with bleeding patterns usually associated with that method. Lochia also will be considered expected.

A pelvic exam must be performed to evaluate all episodes of unexpected genital bleeding. Pelvic exams are not required to evaluate expected bleeding events; however, such exams may be performed at the discretion of the IoR or designee.

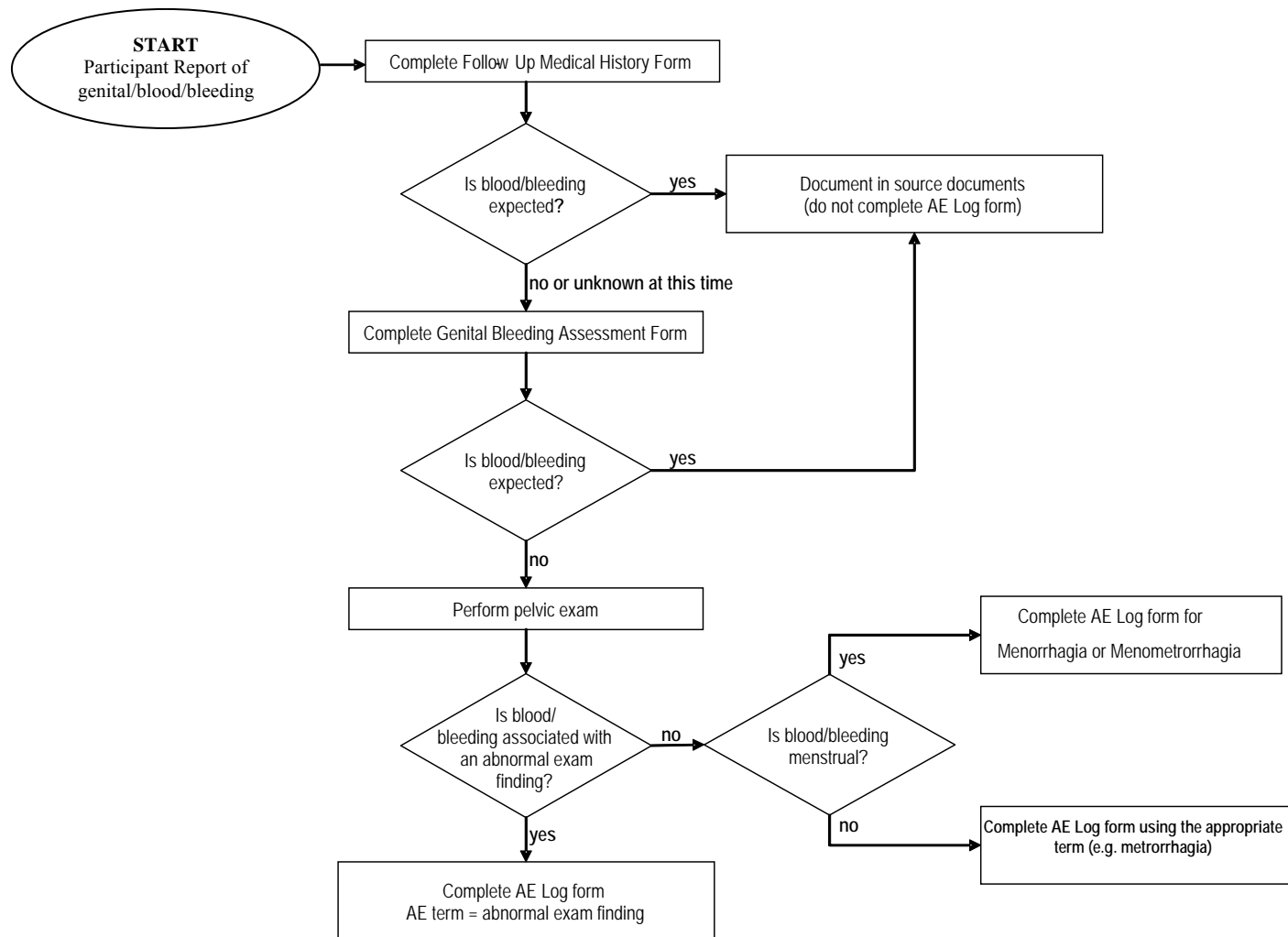
The Genital Bleeding Assessment form must be completed for participants who:

- Self-report genital bleeding other than their normal menses, unless the bleeding is determined to be expected before completing the form
- Do not self-report genital bleeding, but have genital blood/bleeding observed on pelvic exam that is not associated with an abnormal exam finding (e.g., laceration).

The Genital Bleeding Assessment form is not required to be completed for participants who:

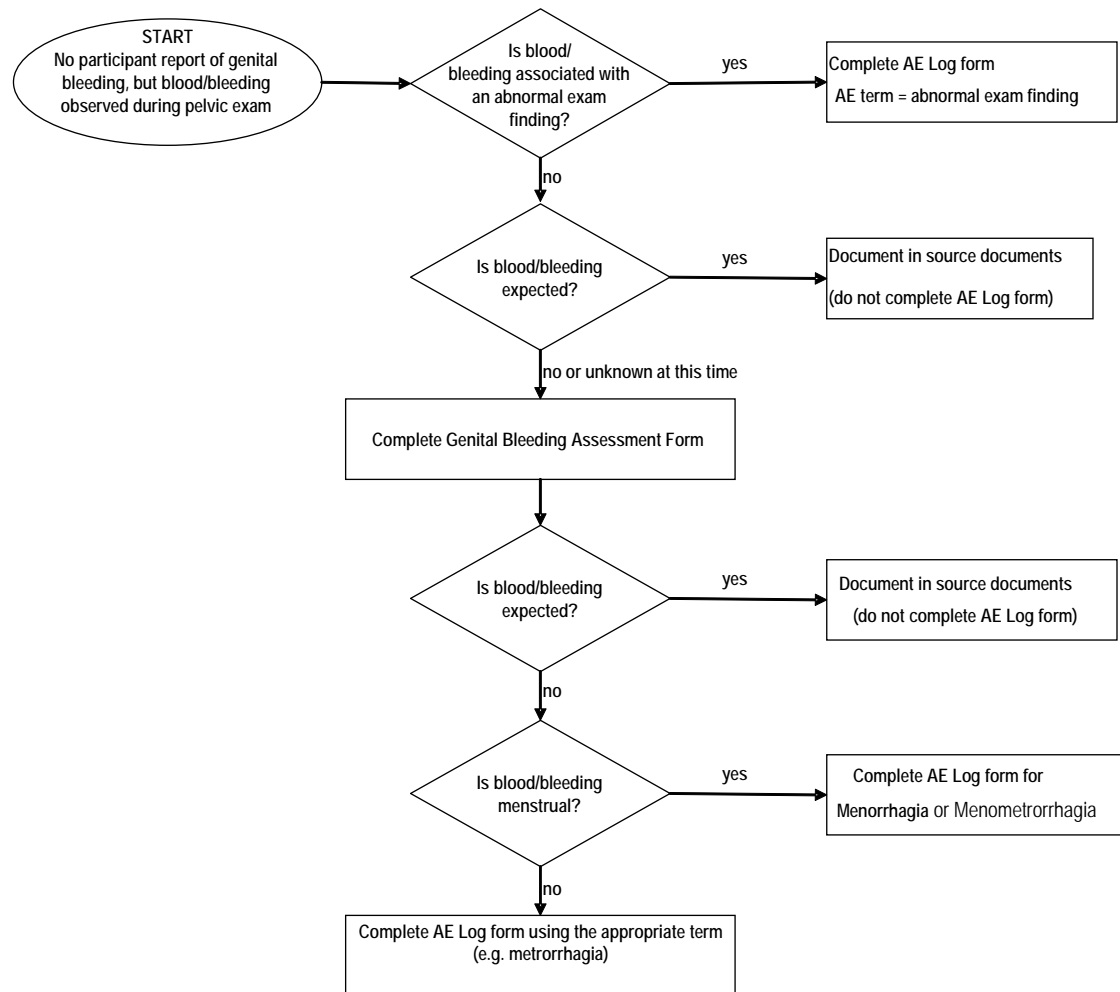
- Self-report genital bleeding that is determined to be expected prior to completion of the form
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is associated with an abnormal exam finding.
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is determined to be menstrual bleeding before completing the form.

Figure 10-2a
 Overview of Assessment and Reporting Procedures for Genital Bleeding in MTN 004 — Beginning with Participant Report of Bleeding



Note: This algorithm is followed for non-pregnant participants only (see Section 10.6) and does not apply to genital hemorrhage. See Section 10.6.4 for more information on terminology and severity grading for adverse events (AEs) involving genital bleeding.

Figure 10-2b
 Overview of Assessment and Reporting Procedures for Genital Bleeding in MTN 004 — Beginning with Clinical Observation of Blood/Bleeding



Note: This algorithm is followed for non-pregnant participants only (see Section 10.6) and does not apply to genital hemorrhage. See Section 10.6.4 for more information on terminology and severity grading for adverse events (AEs) involving genital bleeding.

10.6.4 Documentation of Genital Bleeding

Participants' prior history of menstrual and non-menstrual genital bleeding will be documented on the non-DataFax Baseline Medical History form and on the Pre-existing Conditions case report form, if applicable.

All cases of participant-reported genital bleeding occurring between usual menstrual periods will be documented on the Follow-up Genital Symptoms form. All clinically observed genital blood/bleeding will be documented on the Pelvic Exam Diagrams form and the Follow-up Pelvic Exam form. In addition, certain episodes of genital bleeding will be documented on the Genital Bleeding Assessment form, as specified in Section 10.6.3 above.

All episodes of unexpected menstrual bleeding and unexpected non-menstrual genital bleeding — whether participant-reported or clinician-observed or both — will be considered adverse events (AEs) that must be documented on Adverse Experience Log case report forms. Detailed information on AE reporting is provided in Section 11, however when reporting genital bleeding events, reference also should be made to the points below, which standardize the terminology that should be used at all sites when reporting AEs involving genital bleeding.

- Expected menstrual bleeding should not be reported as an AE. “Early menses” also should not be reported as an AE. Although clinical judgment will be required to determine whether any genital bleeding event may be due to early menses, as a general guideline, menses occurring more than two days prior to the participant’s usual menstrual cycle should be considered early menses. It is recognized, however, that it may not be possible to make a real-time diagnosis of early menses, based on the information available when first documenting a genital bleeding event. For example, the event could be reported on the first day of bleeding and it may not be known at that time whether a full menstrual period will follow. When information needed for a real time diagnosis of early menses is not available, study clinicians should initially report the event using a term other than “early menses” and then review the event after its final outcome has been ascertained and determine whether it should be re-categorized as “early menses.”
- Unexpected menstrual bleeding (i.e., menstrual bleeding that is heavier in volume or of longer duration than the participant’s usual menses), should be reported as an AE using the following AE term:
 - Menorrhagia: prolonged (more than seven days) or excessive (more than 80 mL) uterine bleeding
 - Menometrorrhagia: prolonged uterine bleeding occurring at irregular intervals

Grade these AEs per the “Menorrhagia” row of the Female Genital Grading Table .

- Expected non-menstrual bleeding should not be reported as an AE.

- Unexpected non-menstrual bleeding that is associated with an observed abnormal pelvic exam finding should be reported as an AE using the term associated with the exam finding, with the anatomical location noted. For example, if a laceration is observed on exam, with blood emanating from the finding, the term “laceration” should be used to describe the AE. The fact that blood or bleeding was present also will be documented on the Pelvic Exam Diagrams form and the Pelvic Exam case report form, and may be noted in the Comments section of the Adverse Experience Log form, but the term “metrorrhagia” (“intermenstrual bleeding”) should not be used to describe the AE.
- Unexpected non-menstrual bleeding that is not associated with an observed pelvic exam finding, i.e., for which no abnormal source of blood or bleeding is observed on exam, should be reported as an AE using the term “metrorrhagia.” This term refers to bleeding of variable amounts occurring between regular menstrual periods and should be used to report all types of unexpected non-menstrual bleeding such as prolonged or excessive uterine bleeding, spotting between menses, ovulation bleeding, vaginal spotting, and breakthrough bleeding. This term also should be used to report blood-tinged discharge and blood observed in the vagina with no identified source. Grade these AEs per the “Metrorrhagia” row in the Female Genital Grading Table.
- In cases with bleeding that qualifies as both menorrhagia and metrorrhagia, it should be labeled menometrorrhagia, but will be graded based on the menorrhagia component. For example, if a participant experiences genital bleeding at irregular intervals that is heavier than her usual menses, you will report the event as “menometrorrhagia” and grade per the “Menorrhagia” row in the Female Genital Grading Table.
- If a participant reports genital bleeding after sexual intercourse, you will report this event as “postcoital bleeding” and grade it per the “Postcoital Bleeding” row of the Female Genital Grading Table.
- Genital Hemorrhage should be reported as an AE; however, the term genital hemorrhage should not be used to describe the AE. When reporting genital hemorrhage, a specific location must be specified. To report uterine hemorrhage, the term “uterine hemorrhage” will be used to describe the AE and graded per the menorrhagia row in the Female Genital Grading Table. In the event that a participant experiences a non uterine genital hemorrhage, the specific location of the hemorrhage needs to be included and the term to be used to describe the AE should be the underlying cause of the condition. For example, if the hemorrhage is cause by trauma in the vagina, then it should be graded per the "Vaginal abrasions or lacerations" row, which is graded by extent of laceration not by degree of bleeding.

10.7 STI/RTI Management

Clinical and laboratory evaluations are performed throughout the course of MTN 004 to diagnose the following sexually transmitted diseases and other reproductive tract infections (STIs/RTIs):

- Bacterial vaginosis (BV)
- Candidiasis (any species)
- Chlamydia infection
- Genital ulcer disease

- Gonorrhea infection
- Syphilis infection
- Trichomoniasis

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 10-3. Infections should be considered “symptomatic” when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with “signs” of infection that may be observed during clinical evaluations performed by study staff.

Figure 10-3
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Bacterial vaginosis	Excessive or malodorous discharge is a common finding. Other signs and symptoms include erythema, edema, and pruritis of the external genitalia.
Candidiasis	Clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Symptoms and signs alone do not distinguish the microbial etiology.
Chandroid	The combination of painful ulcer and tender inguinal adenopathy, symptoms occurring in one third patients, suggests a diagnosis of chancoid; when accompanied by suppurative inguinal adenopathy, these signs are almost pathognomonic.
Chlamydia infection	Many infections are asymptomatic and probably chronic. Mucopurulent discharge may not be recognized by the patient or may not be perceived as abnormal.
Genital herpes	Single or multiple vesicles, which usually are pruritic can appear anywhere on the genitalia. Vesicles spontaneously rupture to form shallow ulcers that may be very painful. Lesions spontaneously resolve with minimal scarring.
Gonorrhea infection	Women may have abnormal vaginal discharge, abnormal menses, or dysuria, or most commonly are asymptomatic. Pharyngeal gonorrhea can produce symptoms of pharyngitis.
Syphilis infection — primary	The classical chancre is a painless indurated ulcer located at the site of exposure.
Syphilis infection — secondary	Patients may have a highly variable skin rash, mucous patches, condylomata lata (fleshy, moist tissue growths), lymphadenopathy, alopecia, or other signs.
Syphilis infection — latent	Patients are without clinical signs of infection.
Trichomoniasis	Excessive, frothy, diffuse, yellow-green discharge is common, although clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Dysuria and dyspareunia are also frequent. The type of symptoms or signs alone do not distinguish the microbial etiology.
Pelvic Inflammatory Disease (PID)	Patients must meet three criteria for PID: symptoms and exam findings of lower abdominal pain and tenderness, cervical motion tenderness, and adnexal tenderness. Additionally patients may present with fever, abnormal cervical or vaginal discharge, and cervicitis.
Cervical or Vaginal Warts	Patients usually present with a painless cauliflower lesion(s), sessile or on a stalk. Patients usually present with a painless cauliflower lesion(s), sessile or on a stalk.

Adapted from: *Contraceptive Technology* (18th Revised Edition, 2004); Chapter 8: Reproductive Tract Infections; Alphabetic Catalog of Reproductive Tract Infections; pages 201-218.

10.7.1 STI/RTI Treatment

STIs/RTIs will be treated in accordance with current (2006) CDC Sexually Transmitted Diseases Treatment Guidelines.

Should updated guidelines be issued by the CDC during the study, the updated guidelines will then be followed.

Note: Neither asymptomatic bacterial vaginosis nor asymptomatic vaginal candidiasis require treatment per CDC guidelines.

Figure 10-5 summarizes the 2006 CDC treatment guidelines for each of the conditions listed above. In day-to-day practice, the CDC guidelines — or local site treatment guidelines based on the CDC guidelines — should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, and thereby optimize the validity of study endpoint data, directly observed single dose treatment regimens should be provided whenever possible.

Figure 10-4
(2006) CDC Sexually Transmitted Diseases Treatment Guidelines
for STI/RTI Diagnosed in MTN 004

STI/RTI	CDC Sexually Transmitted Diseases Treatment Guidelines
Bacterial vaginosis	<p><u>For symptomatic patients only.</u></p> <p>Recommended:</p> <ul style="list-style-type: none">• Metronidazole, 500 mg orally twice daily for 7 days <p>Alternative:</p> <ul style="list-style-type: none">• Clindamycin vaginal cream 2%, 5 g intravaginally, at bedtime for 7 days• Metronidazole gel 0.75%, 5 g intravaginally, twice daily for 5 days• Clindamycin, 300 mg orally, twice daily for 7 days• Clindamycin, ovules 100 mg intravaginally once at bedtime for 3 days

Figure 10-4
 (2006) CDC Sexually Transmitted Diseases Treatment Guidelines
 for STI/RTI Diagnosed in MTN 004

STI/RTI	CDC Sexually Transmitted Diseases Treatment Guidelines
Candidiasis	<p><u>For symptomatic patients only.</u> Recommended:</p> <ul style="list-style-type: none"> • Butoconazole 2% cream 5g intravaginally once daily for 3 days <p>Alternative:</p> <ul style="list-style-type: none"> • Butoconazole 2% cream 5g (Butoconazole 1-sustained release), single intravaginal application • Clotrimazole, 1% cream 5g intravaginally, once daily for 7-14 days • Clotrimazole, 100 mg vaginal tablet, once daily for 7 days • Clotrimazole, 100 mg vaginal tablet, two tablets daily for 3 days • Miconazole 2% cream 5g intravaginally, once daily for 7 days • Miconazole 100 mg vaginal suppository, once daily for 7 days • Miconazole 200 mg vaginal suppository, once daily for 3 days • Miconazole 1,200 mg vaginal suppository, once daily for 1 day • Nystatin, 100 000 IU intravaginally, once daily for 14 days • Ticonazole 6.5% ointment 5g intravaginally in a single application • Terconazole 0.4% cream 5g intravaginally, once daily for 7 days • Terconazole 0.8% cream 5g intravaginally, once daily for 3 days • Terconazole 80 mg vaginal suppository, once daily for 3 days • Fluconazole 150 mg orally, one tablet in a single dose
Chlamydia infection (uncomplicated anogenital infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Azithromycin, 1 g orally, as a single dose • Doxycycline, 100 mg orally, twice daily for 7 days (contraindicated in pregnancy and lactation) <p>Alternative:</p> <ul style="list-style-type: none"> • Erythromycin base, 500 mg orally, four times daily for 7 days • Erythromycin ethylsuccinate, 800 mg orally, four times daily for 7 days • Ofloxacin, 300 mg orally, twice daily for 7 days • Levofloxacin, 500 mg orally, once daily for 7 days
Genital herpes (first clinical episode)	<p>Recommended:</p> <ul style="list-style-type: none"> • Acyclovir, 400 mg orally, three times daily for 7-10 days • Acyclovir, 200 mg orally, five times daily for 7-10 days • Famciclovir, 250 mg orally, three times daily for 7-10 days • Valacyclovir, 1000 mg orally, twice daily for 7-10 days
Genital herpes (recurrent episodes of genital lesions)	<p>Recommended:</p> <ul style="list-style-type: none"> • Acyclovir, 400 mg orally, three times daily for 5 days • Acyclovir, 800 mg orally, twice daily for 5 days • Acyclovir, 800 mg orally, three times daily for 2 days • Famciclovir, 125 mg orally, twice daily for 5 days • Famciclovir, 1,000 mg orally, twice daily for 1 day • Valacyclovir, 500 mg orally, twice daily for 3 days • Valacyclovir, 1000 mg orally, once daily for 5 days

Figure 10-4
 (2006) CDC Sexually Transmitted Diseases Treatment Guidelines
 for STI/RTI Diagnosed in MTN 004

STI/RTI	CDC Sexually Transmitted Diseases Treatment Guidelines
Gonorrhea infection (uncomplicated anogenital infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Ceftriaxone, 125 mg IM injection, as a single dose • Cefixime, 400 mg orally, as a single dose • Ciprofloxacin, 500 mg orally, as a single dose (contraindicated in pregnancy, not recommended for children or adolescents) • Ofloxacin 400 mg orally, as a single dose • Levofloxacin, 250 mg orally, as a single dose
Syphilis infection (early infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Benzathine benzylpenicillin, 2.4 million IU, IM injection, at a single session (usually two injections at separate sites) <p>Alternative:</p> <ul style="list-style-type: none"> • Procaine benzylpenicillin, 1.2 million IU, IM injection, daily for 10 consecutive days <p>Alternative for penicillin-allergic non-pregnant patients:</p> <ul style="list-style-type: none"> • Doxycycline, 100 mg orally, twice daily for 14 days • Tetracycline, 500 mg orally, four times daily for 14 days
Trichomoniasis	<p>Recommended:</p> <ul style="list-style-type: none"> • Metronidazole, 2 g orally, as a single dose • Tinidazole, 2 g orally, as a single dose <p>Alternative:</p> <ul style="list-style-type: none"> • Metronidazole, 500 mg orally, twice daily for 7 days

STI/RTI tests of cure are not required in MTN 004; however clinical management of syphilis infections should include repeat serology (RPR) following diagnosis of a new infection to confirm treatment effectiveness. If syphilis is diagnosed during screening, the participant is not eligible for inclusion but should be followed as clinically indicated. Please contact the MTN NL with any questions related to quarterly testing to confirm treatment effectiveness and/or interpretation of unusual syphilis test results.

10.7.2 Screening and Enrollment Considerations

Potential study participants diagnosed during screening with an STI/RTI per 2006 CDC guidelines via laboratory tests will be excluded from enrollment. The only exception to this are women with clinical evidence or laboratory evidence of BV or vulvovaginal candidiasis but who are asymptomatic.

At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are not adequately sensitive and specific for STIs, Pap smear findings associated with STIs should not be considered diagnostic of any infections. Rather, such findings should be handled as follows:

- Do not consider STI-related notations on Pap smear result reports when assessing participant eligibility for the study. Use only the results of protocol-specified STI tests for purposes of eligibility determination.
- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment as needed based on the results of the protocol-specified tests.
- If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the participant's next study visit after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests.

10.7.3 Adverse Event Reporting Considerations

Per the MTN 004 eligibility criteria, no participant may enter the study with an active STI/RTI diagnosed per 2006 CDC guidelines via laboratory tests. Also, no participant may enter the study with a history of STI diagnosis and/or treatment (except HSV recurrence) in the 6 months prior to enrollment. Since no treatable STI or RTI should be recorded as a pre-existing condition for an enrolled participant, any curable STI/RTI identified during follow-up in MTN 004 is considered an AE that must be documented on an Adverse Experience Log case report form. Detailed information on AE reporting is provided in Section 11. When reporting STI/RTI AEs, the severity of the event should be graded according to the "Genitourinary Infections" section of the Female Genital Grading Table (with the exception of asymptomatic bacterial vaginosis).

Genital herpes and genital warts are considered non-curable STIs and are handled differently from the curable STIs. Genital herpes and genital warts are associated with chronic viral infections — HSV-2 and HPV — and periodic symptomatic outbreaks — genital ulcers and genital warts. Reporting of these conditions as pre-existing conditions and/or AEs should be handled as follows:

- If infection with HSV-2 or HPV is known to have occurred before randomization, the infection is considered a pre-existing condition: report on the Pre-existing Conditions form.
- For HPV, genital warts present before randomization are considered a pre-existing condition: report on the Pre-existing Conditions form.
- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was pre-existing before randomization: report on an Adverse Experience Log form.

10.8 Urinary Tract Infections

Dipstick urinalyses will be performed at Screening 1, and when clinically indicated during follow up, to diagnose urinary tract infections (UTI). See Section 12 for details on the required laboratory procedures. Record results on applicable testing log sheets and then transcribe results onto the STI Laboratory Results form.

The following symptoms are considered indicative of a possible UTI:

- Frequent urge to urinate
- Passage of only a small volume of urine
- Pain and burning during urination
- Lower abdominal pain and/or uncomfortable pressure above the pubic bone
- Milky/cloudy, reddish, or bloody urine

When clinically indicated, a urine culture and sensitivity should be performed, and the culture should be documented on the STI Laboratory Results form. The sensitivity test results should be documented in the participant's chart notes only. Once a diagnosis has been made, treatment will be provided per site standards of care and applicable site standard operating procedures (SOPs).

10.9 Product Use Management

For this study, product use management may involve temporarily holding or permanently discontinuing gel use for individual study participants, to protect their safety and well-being while in the study. Product use management in this study will not involve modification of the dose (one applicatorful) or route (intravaginal) of product administration by any participant. It is the responsibility and obligation of the IoR/PI and other authorized study clinicians to assess participants' eligibility for continued product use throughout their participation in the study.

Certain product use management decisions and actions must be undertaken, per protocol, under the direction of the study site IoR/PI. Other product use management decisions and actions are undertaken, under the direction of the IoR/PI, in consultation with the MTN 004 PSRT as described in Section 11.

10.9.1 Circumstances In Which Product Use Must Be Either Temporarily Held or Permanently Discontinued

Product use must be temporarily held in the following circumstances (Refer to Protocol Appendix II):

- Have a pelvic exam finding involving deep epithelial disruption (ulceration) excluding findings observed by colposcopy only
- Have a pelvic exam finding of generalized erythema or severe edema involving an area of more than 50% of the vulvar surface or combined vaginal and cervical surface affected by erythema excluding findings by colposcopy only
- Have abnormal vaginal discharge noted on pelvic exam

- Have presumed cervicitis (findings on exam such as mucopurulent cervical discharge)
- Experience an AE that meets the criteria for expedited reporting to DAIDS (see Section 11 of this manual) that is judged by the IoR or designee to be probably not, possibly, probably, or definitely related to product use. With written approval from the PSRT, participants who experience such an AE may resume product use after the AE resolves (returns to baseline) or stabilizes at a non-reportable severity grade. To obtain approval for resumption of product use from the PSRT, the IoR or designee should submit a query to the PSRT, via the MTN 004 Protocol Safety Physicians, using the MTN 004 PSRT query form as described in Section Appendix 11-3. The PSRT will consider the query and provide a written response (or request more information) via email within three business days.

Product use must be permanently discontinued in the following circumstances:

- Have signs or symptoms of STI(s)/RTI(s) requiring treatment according to the judgment of the investigator
- Experience study product-related toxicity
- Become pregnant or are breastfeeding
- Complete the study regimen as defined in the protocol
- Refuse further study gel use
- Present with any other clinical reason to discontinue study product use, as determined by the IoR/PI.
- Experience a Grade 4 EAE that is judged by the site investigator or designee to be definitely, probably, possible, or probably not related to the study gel or applicator
- Because a herpetic outbreak is a self-limited condition in an immunocompetent host, a participant who experiences a herpes outbreak does not necessarily require treatment. In such cases, a treatment decision will be made based on the clinician's and participant's assessments. If treatment is provided, participants will be permanently discontinued from study product. If treatment is not warranted, participants may continue study product.

Per protocol, participants at all study sites will continue to be followed as a study participant regardless if they have had study gel temporarily held or permanently discontinued.

10.9.2 Circumstances In Which Product Use May Be Either Temporarily Held or Permanently Discontinued

Product use may be either temporarily held or permanently discontinued, at the discretion of the IoR, under the following circumstances, in consultation with the PSRT:

- The participant is unable or unwilling to comply with required study procedures
- The participant might otherwise be put at undue risk to her safety and well-being by continuing product use

10.9.3 Documentation of Product Use Management

All product use management decisions must be thoroughly documented in participant's study charts. It is expected that signed and dated chart notes, together with correspondence to and from the PSRT, when applicable, will serve as the primary source documentation for these decisions; however other site-specific source documents also may be used. In addition to this documentation, product holds should be communicated to study pharmacy staff using the MTN 004 Study Gel Request Slip, as described in Section 6 and a Product Hold/Discontinuation case report form should be completed and faxed to the MTN SDMC, as described in Section 14.

10.9.4 Participant Follow-Up During Periods of Product Use Discontinuation

Participants who either temporarily or permanently discontinue product use will not routinely be withdrawn from the study. Rather, every effort will be made to complete all protocol-specified follow-up visits and procedures with these participants (with the exception of product-related procedures that are not applicable during the period of product use discontinuation).

10.9.5 Collection of Product Supplies During Periods of Product Use Discontinuation

If a participant becomes pregnant or experiences an adverse event that requires permanent discontinuation of product use, any unused applicators remaining in her possession should be collected from her as soon as possible and returned to the pharmacy on the day of collection.

It is not necessary to collect remaining unused (unopened) applicators from participants for whom gel use is temporarily held for an expected short period of time. However, applicators may be collected from such participants, to protect their safety, if it is suspected that the participant may not comply with clinic staff instructions to refrain from gel use for the duration of the temporary hold.

For all product holds requiring collection of unused applicators, if the applicators are not collected within five working days of initiating the product hold, the MTN 004 PSRT must be informed, using the PSRT Query Form as described in Section Appendix 11-3. When informing the PSRT, please describe the reason for the product hold, actions taken to try to collect the unused applicators, and plans and timelines for further action to collect the applicators.

10.10 Pregnancy Management

Please refer to the Section 6 of this manual for procedural instructions for management of participant pregnancies that may occur during follow-up.

Section Appendix 10-1

Scenarios for AE Grading using Female Genital Grading Table for Use in Microbicide Studies

10-1.1 During the Screening/Enrollment Visit, Ms. X reports that her menses usually occur every four weeks and last for five to seven days. She gives no previous history of intermenstrual or prolonged/heavy bleeding. When she returns for her final Three-Week Clinic Visit, she reports that her menses started that day, approximately one week earlier than expected. What procedures should be followed?

- Depends on the clinician's judgment. If the clinician considers this event to be early onset menses of menses, this event should not be reported as an AE. However, if the clinician considers this event to be unexpected bleeding, then report this genital bleeding as an AE using the term metrorrhagia and grade according to the Female Genital Grading Table under "Abnormal Uterine Bleeding Unrelated to Pregnancy". The Clinician should perform a pelvic exam for further evaluation.

Why? This event is considered metrorrhagia if it is unexpected (i.e. her baseline history does not have any previous history of intermenstrual bleeding).

10-1.2 Continuing from the scenario above, suppose the clinician judged the genital bleeding to be unexpected and decided to conduct a safety visit post termination to follow up on the AE of metrorrhagia. At the follow up Safety Visit, nine days later the participant is still bleeding. What would you do?

- Update the AE log to change the previous report of metrorrhagia to an AE of menometrorrhagia, and grade according to menorrhagia row in the Female Genital Grading Table under "Abnormal Uterine Bleeding Unrelated to Pregnancy". The clinician should perform a pelvic exam for further evaluation. The clinician should attempt to follow this AE until resolution (post termination).

Why? The prolonged menses is part of the same bleeding event reported on the previous visit; therefore the term used to describe this event needs to be updated to reflect the participant's current bleeding symptoms. Grade this event per the Female Genital Grading table.

10-1.3 Ms. Y reports at her Two-Week Clinic Visit that she had menstrual cramps during her last period that were so painful that she stayed home from work, in bed, for two days. Generally this participant has very mild menstrual symptoms, if any. What would you do?

- Report this event as an AE using the term dysmenorrhea and grade according to the "Dysmenorrhea" row of the Female Genital Grading Table. The Clinician should perform a pelvic exam for further evaluation.

Why? The reported menstrual cramps are a change from this participant's baseline menstrual symptoms. It is important that the clinician evaluates if there is an anatomical reason why the participant is having pain.

Section Appendix 10-1

Scenarios for AE Grading using Female Genital Grading Table for Use in Microbicide Studies

10-1.4 Suppose instead, Ms. Y reports to the Clinic at her Two-Week Clinic Visit and reports that two days ago, she experienced some vaginal spotting after having sex with her partner. What would you do?

- Report this event as an AE of Postcoital Bleeding, and grade according to the “Postcoital Bleeding” row in the Female Genital Grading Table. Clinician should perform a pelvic exam for further evaluation (e.g. anatomical location of bleed).
- If the clinician identifies the anatomical source of bleeding, the adverse event should be reported using the anatomical site (e.g., cervical friability)

Why? Postcoital bleeding is considered unexpected non-menstrual bleeding, and should be considered an AE. The term “metrorrhagia” (intermenstrual bleeding) *should not* be used to describe this AE.

10-1.5 Ms. Z reported at baseline that her usual menstrual cycle is about 29 days and that she usually has 8 menstrual bleeding days per cycle. At her last weekly visit, Ms. X reported that her last menses lasted 9 days. Should this be reported as an AE?

- If the reported length of bleeding is greater than baseline, you must grade according to the “Menorrhagia” row under “Abnormal Uterine Bleeding Unrelated to Pregnancy” in the Female Genital Grading Table and determine whether an increase in severity has occurred. If there is an increase in severity you would need to report the occurrence of menorrhagia at the higher severity grade as an AE.

Why? Ms. Z should be considered to have menorrhagia as a pre-existing condition (menses lasting longer than 7 days). At baseline you will need to grade the pre-existing menorrhagia based on the guidance provided in the Female Genital Grading Table under “Abnormal Uterine Bleeding Unrelated to Pregnancy” and record the grade on the Baseline Medical History form and Pre-Existing Conditions form. By having this information recorded on the Baseline Medical History form and Pre-Existing Conditions form, you will be able to assess whether or not an AE has occurred and the grade of the AE.

Section Appendix 10-1

Scenarios for AE Grading using Female Genital Grading Table for Use in Microbicide Studies

10-1.6 At her Two-Week Clinic Visit, Ms. P has a positive pregnancy test. She discontinues study gel use per protocol, but she agrees to stay in the study for follow up. At her Three-Week Clinic Visit, she reports genital bleeding. What should you do?

- Take a detailed history and determine whether the bleeding, and possible abortion, was induced or spontaneous.
- Report this AE using clinically appropriate terminology reflecting the cause or source of the bleeding. If this is a spontaneous abortion, use the correct terminology including the term spontaneous. Grade this AE according to the “Complications of Pregnancy” section of the Female Genital Grading Table. The participant should be referred to a qualified clinician for further evaluation, care and treatment.
- If this is an elective abortion (e.g. the patient took an herbal inducement) this would not be an adverse event and should only be reported if the bleeding is unexpected.

Why? The term “metrorrhagia” (intermenstrual bleeding) should not be used in this case because the participant is pregnant, and the bleeding may be associated with complication in pregnancy.

10-1.7 Suppose Ms. W reports at her One-Week Clinic Visit she had a vaginal itching, rash, and vaginal discharge two days before the clinic visit. On the day of the visit, the clinician performs a pelvic exam and notices an area with erythema and another area with edema. What do you do?

- Determine if all these signs and symptoms could be group together as a condition. Since all these symptoms/signs are related, report this event as an AE and grade according to the Female Genital Grading Table under “Composite Signs/Symptom.”

Why? Whenever possible and particularly if two or more signs/symptoms are present, you will use a diagnosis for reporting instead of individual categories.

10-1.8 At her Two-Week Clinic visit, Ms. T reports vaginal discharge. During the pelvic exam, a wet prep is collected for Wet Mount testing. When the wet prep slide is read, yeast is observed. What do you do?

- Complete an AE log for Candida or Yeast Vaginitis and grade according to the Genitourinary Infection section of the Female Genital Grading Table. Treat this participant in accordance with current (2006) CDC Sexually Transmitted Diseases Treatment Guidelines, and discontinue this participant from study gel use.

Why? Product is permanently held for this participant because per the MTN 004 protocol, Section 9.4.1, product must be permanently discontinued if the participant has signs or symptoms of STI(s)/RTI(s) requiring treatment according to the judgment of the investigator.

Section 11. Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN 004. Please also refer to Section 8 of the MTN 004 protocol and the Manual for Expedited Reporting of Adverse Events to DAIDS in Appendix IV of the protocol.

11.1 Definitions and General Reporting Guidance

11.1.1 Adverse Event (AE)

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an AE as any untoward medical occurrence in a clinical research participant administered an investigational product and that does not necessarily have a causal relationship with the investigational product. As such, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

The MTN 004 protocol specifies that any untoward medical occurrence experienced by a study participant after randomization is considered an AE, regardless of the study group to which the participant is assigned. Therefore AEs must be identified, documented, and followed to resolution for MTN 004 participants in all three study arms. Source documentation for each AE should minimally include the following information: AE term/diagnosis, severity grade, onset date, outcome, outcome date, and treatment.

Medical conditions, problems, signs, symptoms, and findings identified prior to randomization are considered pre-existing conditions. Such conditions should be documented per the screening and enrollment visit guidance provided in Sections 4, 7, and 10 of this manual, and reported on the Pre-Existing Conditions case report form (see Section 14). If a pre-existing condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE.

11.1.2 Reportable Adverse Events

Per Version 3.0 of the MTN 004 protocol, study staff will report on case report forms the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs
- All serious AEs, as defined by ICH-E6 (see also Section 11.1.3)
- All AEs of severity grade 1 or higher (see also Section 11.3)
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited AE reporting requirements (see also Section 11.1.4)

The category of genital, genitourinary, and reproductive system AEs includes AEs involving the vulva, vagina, cervix, uterus, Fallopian tubes, ovaries, breasts, anus, rectum, kidneys, ureters, urethra, and bladder. All AEs associated with abnormal pelvic exam findings are considered to fall in this category. All fetal losses — including spontaneous fetal deaths, still births, spontaneous abortions, and ectopic pregnancies — are considered reproductive system AEs. Elective abortions are not considered AEs; however, complications or untoward sequelae of elective abortions are considered reproductive system AEs. For pregnant participants, AEs that are related to the pregnancy, worsened by the pregnancy, or require changes in clinical management of the pregnancy are considered reproductive system AEs. For example, nausea and vomiting related to pregnancy (hyperemesis) are considered reproductive system AEs, but nausea and vomiting due to gastroenteritis during pregnancy are not. Chronic hypertension worsened by pregnancy would be considered a reproductive system AE, as would diabetes previously controlled by diet that requires insulin during pregnancy.

The Adverse Experience Log case report form (see Section 14) is used to report the above-listed reportable AEs to the MTN Statistical and Data Management Center (SDMC) via DataFax. All study sites are strongly encouraged to utilize AE tracking tools to ensure that all AEs are source documented and that all reportable AEs are reported to the MTN SDMC on the Adverse Experience Log form.

Source documentation for all AEs should minimally include the following information: AE term/diagnosis, severity grade, onset date, outcome, outcome date, and treatment. For reportable AEs, the following additional data elements also must be source documented: date reported to site, relationship to study product, action taken with study product as a result of the AE, whether the AE is serious per ICH-E6 (see Section 11.1.3), and whether the AE meets expedited AE reporting requirements (see Section 11.1.4). Each site's SOP for source documentation should define the extent to which the Adverse Experience Log form will be used as the source document for these data elements.

Site-specific delegation of duties documentation should designate study staff authorized by the Investigator or Record (IoR) to complete Adverse Experience Log forms. Regardless of who initially completes these forms, a clinician listed on the site's FDA Form 1572 should review them to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

11.1.3 Serious Adverse Event (SAE)

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongs an existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious and that “important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above” should also usually be considered serious.

SAEs are a subset of all AEs. All SAEs are reportable AEs. The Adverse Experience Log case report form includes an item (item 8) to record whether this is considered an SAE. For each AE identified in MTN 004, an authorized study clinician must determine whether the AE meets the definition of SAE. If the adverse event is determined to be a serious adverse event but DOES NOT ALSO MEET THE CRITERIA OF AN EAE (see Section 11.1.4), an SAE form (see Appendix 11-3) must be completed and faxed within one business day of the site awareness of the SAE to:

Clare Price
Clinical Development Manager
Starpharma Pty Ltd
F: +61 3 9510 5955

Baker Building, 75 Commercial Rd
Melbourne VIC 3004 Australia
Postal Address:
PO Box 6535
St Kilda Road Central VIC 8008 Australia
T: +61 3 8532 2712,
M: 0438 007135 W: www.starpharma.com
Email : clare.price@starpharma.com

11.1.4 Expedited Adverse Event (EAE)

Expedited adverse events (EAEs) are AEs that meet criteria specified in the study protocol as requiring additional reporting for rapid review and assessment by DAIDS. In some cases, DAIDS may be required to report the EAE to the US Food and Drug Administration (FDA). DAIDS policy requires that EAEs be reported to the DAIDS Safety Office within three business days of site awareness of the EAE, however for MTN-004, sites will submit EAE to DAIDS within one business day. Sites will also submit EAE to Starpharma Pty Ltd within one business day of the site awareness of the EAE. All EAEs must be reported on a DAIDS Expedited Adverse Event (EAE) Form. Copies of the form and form completion instructions are available at <http://rcc.tech-res-intl.com>.

Although seriousness is a consideration in determining whether an AE meets the definition of EAE, the terms SAE and EAE are not synonymous. The two terms refer to two different, but overlapping, subsets of AEs. For MTN 004, the subset of AEs that are considered EAEs includes some AEs that are serious and some that are not serious.

The Manual for Expedited Reporting of Adverse Events to DAIDS defines levels of EAE reporting that may be used in DAIDS-sponsored studies. For MTN 004, the “intensive” reporting level must be followed in this Phase I study.

A study physician listed on the site's FDA Form 1572 must review and verify all data recorded on the DAIDS EAE Form for accuracy and completeness. This physician also must make the final assessment of the relationship between the EAE and study product and sign the completed form. If necessary to meet required reporting timeframes, an EAE Form may be submitted to the DAIDS Safety Office without a completed signature page. However, the completed signature page, and any necessary corrections or additions, must be submitted to the DAIDS Safety office and Starpharma Pty Ltd within one business day.

The DAIDS Safety Office fax number is shown on the first page of the EAE Form. Completed forms also may be digitally scanned and submitted to the DAIDS Safety Office via email. Contact details are as follows:

Website:	http://rcc.tech-res-intl.com
Phone:	301-897-1709 or toll free in the US: 800-537-9979
Fax:	301-897-1710 or toll free in the US: 800-275-7619
Email:	RCCSafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM ET

The DAIDS Safety Office will email a confirmation of receipt for each EAE Form received. If a confirmation of receipt is not received within 24-48 hours after submission, study sites should contact the Safety Office for more information and/or re-submit the EAE Form.

The completed EAE form must also be faxed within one business day of the site awareness of the EAE to:

Clare Price
Clinical Development Manager
Starpharma Pty Ltd
F: +61 3 9510 5955

Baker Building, 75 Commercial Rd
Melbourne VIC 3004 Australia
Postal Address:
PO Box 6535
St Kilda Road Central VIC 8008 Australia
T: +61 3 8532 2712,
M: 0438 007135 W: www.starpharma.com
Email : clare.price@starpharma.com

With the exception of congenital anomalies and birth defects identified among infants born to study participants, all EAEs are reportable AEs that must also be reported on Adverse Experience Log case report forms. When completing Adverse Experience Log case report forms and EAE Forms, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness, and consistency. All AE descriptions and details (e.g., onset date, severity grade, relationship to study product) must be recorded consistently across all documents. All EAE Forms received at the DAIDS Safety Office will be compared with Adverse Experience Log forms received at the MTN SDMC to ensure that all reports that should have been received by both the DAIDS Safety Office and the SDMC have been received and that the details recorded on each form are consistent.

11.1.4.1 EAEs for MTN 004 Participants

EAE reporting requirements for MTN 004 are presented in Figure 11-3.

Figure 11-3 Expedited Adverse Event Reporting Requirements for MTN 004	
Type of Adverse Event	Phase I: Intensive EAE Reporting
Results in death	Report as EAE regardless of relationship to study product
Is a congenital anomaly or birth defect or fetal loss	Report as EAE regardless of relationship to study product
Results in persistent or significant disabilities or incapacities	Report as EAE regardless of relationship to study product
Requires or prolongs hospitalization or requires intervention to prevent significant/permanent disability or death	Report as EAE if relationship to study product is: <ul style="list-style-type: none"> • Definitely related • Probably related • Possibly related • Probably not related
Is life-threatening (includes all Grade 4 AEs)	Report as EAE if relationship to study product is: <ul style="list-style-type: none"> • Definitely related • Probably related • Possibly related • Probably not related
Other Grade 3 AEs	Report as EAE if relationship to study product is: <ul style="list-style-type: none"> • Definitely related • Probably related • Possibly related • Probably not related
Other Grade 1 and Grade 2 AEs	Do not report as EAE

In addition to the events listed above, the following also should be reported as EAEs:

- AEs that may be related to study product (i.e., definitely, probably, possibly, or probably not related) that the IoR believes are of sufficient concern to be reported on an expedited basis to DAIDS. This includes AEs that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent a serious AE.

- Serious AEs that are not related to study product but could be associated with study participation or procedures.
- Unexpected serious AEs that may be related to study product (i.e., definitely, probably, possibly, or probably not related) that occur after the participant's study exit visit.

11.2 Adverse Event Terminology

Study staff must assign a term or description to all AEs identified in MTN 004. Whenever possible, a diagnosis should be assigned, rather than a cluster of signs and/or symptoms. When relevant, an anatomical location should be included in the term or description. This is especially important in MTN 004 for distinguishing pelvic exam findings that may be observed on the vulva, in the vagina, or on the cervix.

When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be reported as an individual AE.

If an abnormal laboratory test result is reported as an AE, separate from any clinical diagnosis associated with the result, the type of test performed and the direction of the abnormality should be reported (e.g., elevated ALT). The severity grade of the result should not be reported as part of the AE description since the grade is captured elsewhere (item 3) on the form.

11.3 Adverse Event Severity

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN 004 must be graded on a five-point scale:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Potentially life-threatening
- Grade 5 = Death

Severity is not the same as seriousness, which is based on the outcome or action associated with an event, as described in Section 11.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004, Addendum 1 (The Female Genital Grading Table for Use in Microbicide Studies), will be the primary tool for grading adverse events for this study, with the exception of asymptomatic bacterial vaginosis which will not be a reportable AE. Adverse events not included in Addendum 1, the Female Genital Grading Table, will be graded by the DAIDS Table for Grading Adult and Pediatric Adverse Events Version 1.0, December 2004. In cases where an AE is covered in both tables, the Female Genital Grading Table will be the grading scale utilized.

11.3.1 Answers to Frequently Asked Questions About Severity Grading

- If the severity of an AE falls into more than one grading category on the Female Genital Grading Table, assign the higher of the two grades to the AE.
- Laboratory values that fall outside of a site’s normal range, but do not meet criteria for grade 1 severity, should not be considered “abnormal” for purposes of reporting pre-existing conditions or AEs, unless clinical judgment determines otherwise.
- Conditions and laboratory abnormalities that are not explicitly listed on the Female Genital Grading Table should be graded according to the “estimating severity grade” row of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.
- Seasonal allergies should be graded according to the “estimating severity grade” row of the DAIDS AE Grading Table (not the “acute systemic allergic reaction” row).
- If systemic antimicrobial treatment is given to treat an STI/RTI, the grade must be 2 or higher.
- Spontaneous abortions should be graded according to the “First Trimester Bleeding” row of the Female Genital Grading Table.

11.4 Adverse Event Relationship to Study Product

For each reportable AE identified in MTN 004, an authorized study clinician must assess the relationship of the AE to study product, based on the temporal relationship of the AE to administration of product, product pharmacology and other information provided in the Investigator’s Brochures, and clinical judgment. One of the following relationship categories must be assigned to each reportable AE:

- **Definitely Related:** The AE and administration of study gel are related in time, and a direct association can be demonstrated.
- **Probably Related:** The AE and administration of study gel are reasonably related in time, and the AE is more likely explained by study gel than other causes.
- **Possibly Related:** The AE and administration of study gel are reasonably related in time, and the AE can be explained equally well by causes other than study gel.
- **Probably Not Related:** A potential relationship between the AE and study gel could exist (i.e., the possibility cannot be excluded), but the AE is most likely explained by causes other than study gel.
- **Not Related.** The AE is clearly explained by another cause not related to study gel.

***Note:** The MTN 004 study products are comprised of the gel applicators as well as the gel contained in each applicator. Any AEs thought to be related to an applicator should be documented as such by choosing one of the “related” categories and using descriptive text, comments, or other notations to indicate that the presumed relationship is to the applicator.*

In addition to the relationship categories listed above, DAIDS allows a relationship of “pending” to be temporarily assigned to AEs that result in death, if additional time and information are needed to determine the relationship of the AE to study product. However, a final relationship assessment must be submitted to DAIDS (via the EAE Form) within one business day after first reporting the death. If a final assessment is not made within one business day, the AE will be considered possibly related to study product.

11.5 Adverse Event Outcomes and Follow-Up Information

All AEs identified in MTN 004 must be followed clinically until the AE resolves (returns to baseline) or stabilizes. In addition to performing other protocol-specified procedures, at each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs and evaluate and document their current status. Outcomes must also be reported on Adverse Experience Log case report forms. In many cases the final outcome of an AE will not be available when the Adverse Experience Log form is first completed and faxed to DataFax. In such cases, the form should be updated when the final outcome becomes available and re-faxed to DataFax at that time.

If an AE increases in severity or frequency (worsens) after it has been reported on an Adverse Experience Log case report form, it must be reported as a new AE, at the increased severity or frequency, on a new Adverse Experience Log case report form. In this case, the outcome of the first AE will be documented as “severity/frequency increased.” The outcome date of the first AE and the onset date of the new (worsened) AE will both be the date upon which the severity or frequency increased.

Site staff are not required to report the outcome of EAEs to the DAIDS Safety Office, unless outcome information is specifically requested by DAIDS. However, if an EAE increases in severity to a higher grade than previously reported, it must be reported to the DAIDS Safety Office as a new EAE on a new EAE Form.

EAE follow-up information also must be reported to the DAIDS Safety Office under the following circumstances:

- Requests from DAIDS for additional information
- A change in the relationship between the AE and study product by the study physician
- Additional significant information that becomes available for a previously reported adverse event (this is particularly important for new information addressing cause of death if the initial assignment was “pending”)
- Results of re-challenge with the study product, if performed

In these circumstances, the required follow-up information should be reported on a new EAE Form as a Follow-Up Report. See also Section 5 of the Manual for Expedited Reporting of Adverse Events to DAIDS.

11.6 Reporting Recurrent Adverse Events

If an AE that was previously reported on an Adverse Experience Log case report form resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new Adverse Experience Log case report form.

An important clarification of this guidance for MTN 004 relates to genital herpes.

- If infection with HSV-2 occurred before randomization, the infection is considered a pre-existing condition: report on the Pre-existing Conditions form.
- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was pre-existing before randomization: report on an Adverse Experience Log form.

If an EAE that was previously reported to the DAIDS Safety Office resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported to the DAIDS Safety Office as a new EAE on a new EAE Form.

11.7 Social Harms

In addition to medical AEs, participants in MTN 004 may experience social harms — non-medical adverse consequences — as a result of their participation in the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends. They also could experience stigma or discrimination from family members and members of their community. In the event that any social harms occur, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section.

Prior to study initiation, study staff teams at each site should discuss as a group, and with community representatives, what issues and problems are most likely to be encountered by participants at their site, and should agree upon how these issues and problems should be handled if reported. Roles and responsibilities should be defined for all staff members, such that each staff member is aware of what actions he/she can appropriately take, and what actions should be referred to other members of the team. During study implementation, staff teams at each site should continue to discuss actual participant experiences, successful and unsuccessful response strategies, and other lessons learned among themselves and with community representatives. Based on these discussions and lessons learned, procedures for responding to issues and problems should be reassessed and updated as needed throughout the study.

The following are suggested strategies for responding to social harms that may be adapted and tailored to best meet participant needs at each site:

- When first responding to an issue or problem, actively listen to the participant's description of the problem and ask questions to elicit as much detail as possible about the problem, including the participant's perception of the severity of the problem. Record all pertinent details in signed and dated chart notes. If the issue or problem meets criteria for expedited reporting to the DAIDS Safety Office, report it as described in Section 11 above. Also report the issue or problem to all responsible IRBs/ECs, if required per IRB/EC guidelines.
- Ask the participant to articulate her thoughts on what can/should be done to address the problem, including what she would like study staff to do in response to the problem (if anything).
- Discuss with the participant any additional or alternative strategies that you might suggest to address the problem and collaborate with her to develop a plan to try to address the problem. Document the plan in signed and dated chart notes.
- Take all possible action to try to address the problem, per the plan agreed upon with the participant. Document all action taken, and outcomes thereof, in signed and dated chart notes.
- As with medical AEs, follow all problems to resolution or stabilization.
- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.
- Consult the MTN 004 Protocol Safety Review Team (PSRT) for further input and guidance as needed.

As is the case with medical AEs, data collected on social harms will be monitored by the MTN 004 PSRT and the NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB), as described below.

11.8 MTN 004 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN 004 protocol and Section 14 of this manual for a complete description of the participant safety monitoring procedures in place for MTN 004. Also refer to Section 15 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN 004 safety monitoring procedures.

Participant safety is of paramount importance in MTN 004. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study site staff, under the direction of the IoR. The IoR and designated site staff also are responsible for submitting case report forms to the MTN SDMC and EAE Forms to the DAIDS Safety Office, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- A sub-group of the Protocol Team, including the MTN Safety Physicians, the MTN PI, MTN-004 Protocol Chair, MTN Protocol Specialist, FHI Clinical Research Manager, Statistical Data Management Center (SDMC) Clinical Affairs Research Nurse, SDMC Project Manager, all Site IoR/PIs, DAIDS and NICHD Medical Officers and the DAIDS Clinical Operations Study Coordinator, will serve as the Protocol Safety Review Team (PSRT). However, a quorum for PSRT calls will consist of only the DAIDS and NICHD Medical Officers and one of the MTN Safety Physicians. Close cooperation between the PSRT and other study team members will be necessary to monitor participant safety and respond to occurrences of toxicity in a timely manner.
- A multi-tiered safety review process will be followed for the duration of this study. The review process, which is both timely and extensive in scope, includes review of medical history information, clinical and laboratory AEs and concomitant medications. The study site investigators are the first layer of this tiered system and are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise. Additional special reviews may also be conducted as dictated by the occurrence of certain events.
- The SDMC Clinical Affairs Research Nurse represents the second tier. This research nurse will review incoming safety data on an ongoing basis. Values identified during review that are considered questionable, inconsistent, or unexplained will be queried for verification.
- All EAE reports submitted to the DAIDS Safety Office will be synchronously sent by the sites to Starpharma, DAIDS Medical Officer, NICHD Medical Officer, SDMC Clinical Affairs Research Nurse, and the Protocol Chair for review.
- During the active product use phase of the trial, the PSRT will review clinical and laboratory safety reports (blinded to treatment assignment) and conduct calls every two weeks, or as needed, to review the data as appropriate. The content, format and frequency of these reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to these routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to the MTN representing expertise in the fields of microbicides, biostatistics, and medical ethics may be invited to join the PSRT safety review.
- After the product use and the final safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the MTN-004 PSRT.
- Decisions regarding permanent discontinuation of study gel in individual participants will be made by the PSRT based on careful review of all relevant data and may involve sponsor consultation with the US Food and Drug Administration (FDA).

11.9 Study Product Hold

Accrual and overall study product use for *all* participants will be suspended for a data safety review by the PSRT if any two women enrolled in the study experience the same safety or toxicity endpoint, defined as:

- Having at least one grade 3 or higher adverse experience during follow up judged by the investigator to be definitely, probably, or possibly related to the study gel or applicator,

or

- Having at least one grade 3 or higher macroscopic finding or other clinical evidence (excluding findings observed by colposcopy only) of damage during follow up (judged not to be due to pathogen or iatrogenic trauma) to the vulvar and/or vaginal deep epithelium and/or cervical mucosa including ulceration and other lesions, severe global erythema, and/or severe global edema judged definitely, probably or possible related to the study gel or applicator.

As soon as a site receives information concerning an AE that appears to meet the criteria above, they must first call the SCHARP Safety Phone at 206.786.1343 to report the event.

The SCHARP Safety Phone is monitored 24 hours a day by a SCHARP Clinical Affairs Safety Associate. When calling, sites should be prepared to provide the following information to the SCHARP Safety Associate:

- caller's name and study title (e.g., Nurse Coordinator, site PI)
- site name
- participant ID of participant with AE
- protocol name
- length of time participant has been using study product
- description of the event (onset/resolution dates, severity, work-up performed to date, etc)
- perceived relatedness of the event to study product (applicator and/or gel) per the site PI
- who has evaluated the participant (e.g., site clinician, site PI, doctor off-site)
- any concomitant meds the participant is using
- any pre-existing conditions the participant may have
- site's impression regarding relationship of AE to study product
- site's plan for follow-up and clinical management of participant

Site staff should provide as much detail as possible during this call, as noted above. They also should share any additional information that might help the SCHARP Safety Associate ascertain the participant's condition and health status. For documentation purposes, site staff will also send an email to SCHARP Clinical Affairs (sc.clin.aff@scharp.org) that will contain the same information that was relayed on the call.

When alerted of a safety event, the SCHARP Clinical Affairs Safety Associate determines the severity grade of the event using the Female Genital Grading Table for Use in Microbicide Studies. If the event is not listed in this table, the SCHARP Safety Associate will refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS Grading Table) to determine the severity grade of the event. For laboratory value AEs, the SCHARP Clinical Affairs Safety Associate will check the description, value and calculation of severity grade ranges, if applicable, to ensure the accurate grading of the value.

If the SCHARP Safety Associate determines that the criteria for an accrual pause and study-wide product hold are met (see above for criteria), the SCHARP Safety Associate contacts one of the MTN Safety Physicians by telephone as soon as possible to convey the details of the safety events. If the Safety Physician determines that the events may warrant an accrual pause and product hold (regardless of whether or not they meet the protocol criteria), the SCHARP Safety Associate then notifies the DAIDS Medical Officer, NICHD Medical Officer, and Protocol Chair (by phone if possible).

The SCHARP Safety Associate convenes an expedited PSRT review by conference call so that the PSRT can review all relevant safety information. At minimum, the PSRT quorum, consisting of the DAIDS Medical Officer, NICHD Medical Officer, and an MTN Safety Physician, are required to convene the PSRT review call. The PSRT will not consider AEs that are pending, or AEs that are assessed as probably not related or not related to study product when deciding whether or not to institute an accrual pause and study product hold. Per protocol, the PSRT makes the final decision on whether or not to pause study accrual and hold study product for all participants in the study.

If the PSRT decides to pause study accrual and hold study product for all participants, FHI is responsible for promptly notifying the site IoR or designee at all sites. In addition, FHI will send out an official study notification e-mail to the entire protocol team. Staff at each site are responsible for contacting each participant currently using study product at their site. They will instruct these participants to immediately and permanently discontinue study product use and return to the study site as soon as possible to return all unused study product in their possession. Site staff must make every effort to contact each participant personally in order to confirm that she has received and understood instructions to permanently discontinue study product use. Site staff will continue to complete regular study visits for participants in active follow-up. However, sites must immediately discontinue study screening and enrollment activities.

Site staff must complete an AE Log case report form for each reportable AE, and fax the form(s) to SCHARP DataFax within one business day of site awareness of the event(s). Site staff also must complete an EAE or SAE report, if indicated, and must submit the report to the appropriate parties within one business day of site awareness of the event(s). Refer to sections 11.1.3 and 11.1.4 of this manual for more information on reporting and submitting EAE and SAE reports.

Once the relevant AE Log case report forms are faxed to SCHARP DataFax, the SCHARP Safety Associate compares the data recorded on the form with the information provided by the site via phone to identify any discrepancies. The SCHARP Safety Associate may contact the site to address any discrepancies and/or to request further information as needed.

The PSRT holds the responsibility for determining whether to lift a safety pause of accrual and study product use. If and when the PSRT determines to lift the pause, FHI will send official notification via e-mail to the entire protocol team.

11.10 Safety Distributions from DAIDS

Study sites will receive product- and safety-related information throughout the period of study implementation. This information will be distributed by DAIDS, through its Regulatory Compliance Center and/or the MTN Coordinating and Operations Center, and may include:

- Updated Investigator's Brochures
- IND Safety Reports
- DSMB review summaries
- Other safety memoranda and updates

Each distribution will include a cover memo providing instructions on how the document is to be handled. In all cases, a copy of the distribution must be filed in the study site Essential Document files for MTN 004. Also in all cases, study staff responsible for clinical oversight of study participants should be made aware of any newly available safety information. In many cases, the distribution will need to be submitted to all study site IRBs/ECs. Safety distributions do not require IRB/EC approval; however acknowledgement of receipt is desirable. Submission letters/memos for IRB/EC submissions should specify the name and date of all documents submitted.

Section Appendix 11-1
DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

I. Instructions and Clarifications

Grading Adult and Pediatric AEs

The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

Note: In the classification of adverse events, the term "**severe**" is not the same as "**serious**." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

- [Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF](#)
- [Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF](#)
- [Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF](#)

Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges

In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

II. Definitions of terms used in the Table:

Basic Self-care Functions	<u>Adult</u> Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
	<u>Young Children</u> Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	<u>Adult</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.
	<u>Young Children</u> Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm ² – 81cm ²)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm ²)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: in Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to ≥ 180 from > 180 (systolic) and to ≥ 110 from > 110 (diastolic).				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91 st – 94 th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95 th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2 nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1 st degree AV block (PR > normal for age and rate)	Type I 2 nd degree AV block	Type II 2 nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase in interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval \geq 0.50 sec OR Increase in interval \geq 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric \leq 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval \geq 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia- Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia- Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (<u>functional-symptomatic</u>) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – Pediatric ≤ 16 years	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (<u>new onset</u>) – Adult ≥ 18 years See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (<u>known pre-existing seizure disorder</u>) – Adult ≥ 18 years For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent breakthrough seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure – Pediatric < 18 years	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (<u>symptoms</u>) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (<u>clinical exam</u>) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (<u>symptoms</u>) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (<u>clinical exam</u>) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non- ketotic coma)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY <i>Standard International Units are listed in italics</i>				
Absolute CD4+ count – Adult and Pediatric > 13 years (HIV <u>NEGATIVE</u> ONLY)	300 – 400/mm ³ <i>300 – 400/μL</i>	200 – 299/mm ³ <i>200 – 299/μL</i>	100 – 199/mm ³ <i>100 – 199/μL</i>	< 100/mm ³ < 100/μL
Absolute lymphocyte count – Adult and Pediatric > 13 years (HIV <u>NEGATIVE</u> ONLY)	600 – 650/mm ³ <i>0.600 x 10⁹ – 0.650 x 10⁹/L</i>	500 – 599/mm ³ <i>0.500 x 10⁹ – 0.599 x 10⁹/L</i>	350 – 499/mm ³ <i>0.350 x 10⁹ – 0.499 x 10⁹/L</i>	< 350/mm ³ < 0.350 x 10 ⁹ /L
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm ³ <i>1.000 x 10⁹ – 1.300 x 10⁹/L</i>	750 – 999/mm ³ <i>0.750 x 10⁹ – 0.999 x 10⁹/L</i>	500 – 749/mm ³ <i>0.500 x 10⁹ – 0.749 x 10⁹/L</i>	< 500/mm ³ < 0.500 x 10 ⁹ /L
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm ³ <i>1.250 x 10⁹ – 1.500 x 10⁹/L</i>	1,000 – 1,249/mm ³ <i>1.000 x 10⁹ – 1.249 x 10⁹/L</i>	750 – 999/mm ³ <i>0.750 x 10⁹ – 0.999 x 10⁹/L</i>	< 750/mm ³ < 0.750 x 10 ⁹ /L
Infant*†, ≤1 day	4,000 – 5,000/mm ³ <i>4.000 x 10⁹ – 5.000 x 10⁹/L</i>	3,000 – 3,999/mm ³ <i>3.000 x 10⁹ – 3.999 x 10⁹/L</i>	1,500 – 2,999/mm ³ <i>1.500 x 10⁹ – 2.999 x 10⁹/L</i>	< 1,500/mm ³ < 1.500 x 10 ⁹ /L
Comment: Parameter changed from “Infant, < 1 day” to “Infant, ≤1 day”				
Fibrinogen, decreased	100 – 200 mg/dL <i>1.00 – 2.00 g/L</i> OR 0.75 – 0.99 x LLN	75 – 99 mg/dL <i>0.75 – 0.99 g/L</i> OR 0.50 – 0.74 x LLN	50 – 74 mg/dL <i>0.50 – 0.74 g/L</i> OR 0.25 – 0.49 x LLN	< 50 mg/dL < 0.50 g/L OR < 0.25 x LLN OR Associated with gross bleeding

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL <i>5.24 – 6.23 mmol/L</i>	7.5 – 8.4 g/dL <i>4.62–5.23 mmol/L</i>	6.50 – 7.4 g/dL <i>4.03–4.61 mmol/L</i>	< 6.5 g/dL < <i>4.03 mmol/L</i>
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL <i>6.18 – 6.79 mmol/L</i> OR Any decrease 2.5 – 3.4 g/dL <i>1.58 – 2.13 mmol/L</i>	9.0 – 9.9 g/dL <i>5.55 - 6.17 mmol/L</i> OR Any decrease 3.5 – 4.4 g/dL <i>2.14 – 2.78 mmol/L</i>	7.0 – 8.9 g/dL <i>4.34 - 5.54 mmol/L</i> OR Any decrease ≥ 4.5 g/dL > <i>2.79 mmol/L</i>	< 7.0 g/dL < <i>4.34 mmol/L</i>
Comment: The decrease is a decrease from baseline				
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL <i>5.24 – 5.86 mmol/L</i>	7.0 – 8.4 g/dL <i>4.31 – 5.23 mmol/L</i>	6.0 – 6.9 g/dL <i>3.72 – 4.30 mmol/L</i>	< 6.00 g/dL < <i>3.72 mmol/L</i>
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL <i>5.87 - 6.54 mmol/L</i>	8.0 – 9.4 g/dL <i>4.93 – 5.86 mmol/L</i>	7.0 – 7.9 g/dL <i>4.34 – 4.92 mmol/L</i>	< 7.00 g/dL < <i>4.34 mmol/L</i>
Infant*†, ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL <i>7.42 – 8.09 mmol/L</i>	10.0 – 11.9 g/dL <i>6.18 – 7.41 mmol/L</i>	9.0 – 9.9 g/dL <i>5.59- 6.17 mmol/L</i>	< 9.0 g/dL < <i>5.59 mmol/L</i>
Correction: Parameter changed from “Infant < 21 days” to “Infant ≤ 21 days”				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm ³ <i>100.000 x 10⁹ – 124.999 x 10⁹/L</i>	50,000 – 99,999/mm ³ <i>50.000 x 10⁹ – 99.999 x 10⁹/L</i>	25,000 – 49,999/mm ³ <i>25.000 x 10⁹ – 49.999 x 10⁹/L</i>	< 25,000/mm ³ < <i>25.000 x 10⁹/L</i>
WBC, decreased	2,000 – 2,500/mm ³ <i>2.000 x 10⁹ – 2.500 x 10⁹/L</i>	1,500 – 1,999/mm ³ <i>1.500 x 10⁹ – 1.999 x 10⁹/L</i>	1,000 – 1,499/mm ³ <i>1.000 x 10⁹ – 1.499 x 10⁹/L</i>	< 1,000/mm ³ < <i>1.000 x 10⁹/L</i>

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
CHEMISTRIES <i>Standard International Units are listed in italics</i>				
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN <i>30 g/L – < LLN</i>	2.0 – 2.9 g/dL <i>20 – 29 g/L</i>	< 2.0 g/dL <i>< 20 g/L</i>	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN [†]	2.6 – 5.0 x ULN [†]	5.1 – 10.0 x ULN [†]	> 10.0 x ULN [†]
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN <i>16.0 mmol/L – < LLN</i>	11.0 – 15.9 mEq/L <i>11.0 – 15.9 mmol/L</i>	8.0 – 10.9 mEq/L <i>8.0 – 10.9 mmol/L</i>	< 8.0 mEq/L <i>< 8.0 mmol/L</i>
Comment: Some laboratories will report this value as Bicarbonate (HCO ₃) and others as Total Carbon Dioxide (CO ₂). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant*[†], ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL <i>342 – 428 μmol/L</i>	25.1 – 30.0 mg/dL <i>429 – 513 μmol/L</i>	> 30.0 mg/dL <i>> 513.0 μmol/L</i>
Infant*[†], ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL <i>342 – 428 μmol/L</i>	> 25.0 mg/dL <i>> 428 μmol/L</i>
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL <i>2.65 – 2.88 mmol/L</i>	11.6 – 12.5 mg/dL <i>2.89 – 3.13 mmol/L</i>	12.6 – 13.5 mg/dL <i>3.14 – 3.38 mmol/L</i>	> 13.5 mg/dL <i>> 3.38 mmol/L</i>
Infant*[†], < 7 days	11.5 – 12.4 mg/dL <i>2.88 – 3.10 mmol/L</i>	12.5 – 12.9 mg/dL <i>3.11 – 3.23 mmol/L</i>	13.0 – 13.5 mg/dL <i>3.245 – 3.38 mmol/L</i>	> 13.5 mg/dL <i>> 3.38 mmol/L</i>
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL <i>1.95 – 2.10 mmol/L</i>	7.0 – 7.7 mg/dL <i>1.75 – 1.94 mmol/L</i>	6.1 – 6.9 mg/dL <i>1.53 – 1.74 mmol/L</i>	< 6.1 mg/dL <i>< 1.53 mmol/L</i>
Infant*[†], < 7 days	6.5 – 7.5 mg/dL <i>1.63 – 1.88 mmol/L</i>	6.0 – 6.4 mg/dL <i>1.50 – 1.62 mmol/L</i>	5.50 – 5.90 mg/dL <i>1.38 – 1.51 mmol/L</i>	< 5.50 mg/dL <i>< 1.38 mmol/L</i>
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

[†] Use age and sex appropriate values (e.g., bilirubin).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL 5.18 – 6.19 mmol/L	240 – 300 mg/dL 6.20 – 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 years	170 – 199 mg/dL 4.40 – 5.15 mmol/L	200 – 300 mg/dL 5.16 – 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 – 5.9 x ULN [†]	6.0 – 9.9 x ULN [†]	10.0 – 19.9 x ULN [†]	≥ 20.0 x ULN [†]
Creatinine	1.1 – 1.3 x ULN [†]	1.4 – 1.8 x ULN [†]	1.9 – 3.4 x ULN [†]	≥ 3.5 x ULN [†]

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL 6.44 – 8.88 mmol/L	161 – 250 mg/dL 8.89 – 13.88 mmol/L	251 – 500 mg/dL 13.89 – 27.75 mmol/L	> 500 mg/dL > 27.75 mmol/L
Fasting	110 – 125 mg/dL 6.11 – 6.94 mmol/L	126 – 250 mg/dL 6.95 – 13.88 mmol/L	251 – 500 mg/dL 13.89 – 27.75 mmol/L	> 500 mg/dL > 27.75 mmol/L
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL 3.05 – 3.55 mmol/L	40 – 54 mg/dL 2.22 – 3.06 mmol/L	30 – 39 mg/dL 1.67 – 2.23 mmol/L	< 30 mg/dL < 1.67 mmol/L
Infant*[†], < 1 month	50 – 54 mg/dL 2.78 – 3.00 mmol/L	40 – 49 mg/dL 2.22 – 2.77 mmol/L	30 – 39 mg/dL 1.67 – 2.21 mmol/L	< 30 mg/dL < 1.67 mmol/L
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life- threatening consequences	Increased lactate with pH < 7.3 with life- threatening consequences

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

[†] Use age and sex appropriate values (e.g., bilirubin).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

Comment: Added ULN to Grade 1 parameter				
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL 3.37 – 4.12 mmol/L	160 – 190 mg/dL 4.13 – 4.90 mmol/L	≥ 190 mg/dL ≥ 4.91 mmol/L	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL 2.85 – 3.34 mmol/L	130 – 189 mg/dL 3.35 – 4.90 mmol/L	≥ 190 mg/dL ≥ 4.91 mmol/L	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L 0.60 – 0.70 mmol/L	0.9 – 1.1 mEq/L 0.45 – 0.59 mmol/L	0.6 – 0.8 mEq/L 0.30 – 0.44 mmol/L	< 0.60 mEq/L < 0.30 mmol/L
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN 0.81 mmol/L – < LLN	2.0 – 2.4 mg/dL 0.65 – 0.80 mmol/L	1.0 – 1.9 mg/dL 0.32 – 0.64 mmol/L	< 1.00 mg/dL < 0.32 mmol/L
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL 0.97 – 1.13 mmol/L	2.5 – 2.9 mg/dL 0.81 – 0.96 mmol/L	1.5 – 2.4 mg/dL 0.48 – 0.80 mmol/L	< 1.50 mg/dL < 0.48 mmol/L
Pediatric < 1 year	3.5 – 4.5 mg/dL 1.13 – 1.45 mmol/L	2.5 – 3.4 mg/dL 0.81 – 1.12 mmol/L	1.5 – 2.4 mg/dL 0.48 – 0.80 mmol/L	< 1.50 mg/dL < 0.48 mmol/L
Potassium, serum, high	5.6 – 6.0 mEq/L 5.6 – 6.0 mmol/L	6.1 – 6.5 mEq/L 6.1 – 6.5 mmol/L	6.6 – 7.0 mEq/L 6.6 – 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Potassium, serum, low	3.0 – 3.4 mEq/L 3.0 – 3.4 mmol/L	2.5 – 2.9 mEq/L 2.5 – 2.9 mmol/L	2.0 – 2.4 mEq/L 2.0 – 2.4 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Sodium, serum, high	146 – 150 mEq/L 146 – 150 mmol/L	151 – 154 mEq/L 151 – 154 mmol/L	155 – 159 mEq/L 155 – 159 mmol/L	≥ 160 mEq/L ≥ 160 mmol/L
Sodium, serum, low	130 – 135 mEq/L 130 – 135 mmol/L	125 – 129 mEq/L 125 – 129 mmol/L	121 – 124 mEq/L 121 – 124 mmol/L	≤ 120 mEq/L ≤ 120 mmol/L
Triglycerides (fasting)	NA	500 – 750 mg/dL 5.65 – 8.48 mmol/L	751 – 1,200 mg/dL 8.49 – 13.56 mmol/L	> 1,200 mg/dL > 13.56 mmol/L

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Uric acid	7.5 – 10.0 mg/dL <i>0.45 – 0.59 mmol/L</i>	10.1 – 12.0 mg/dL <i>0.60 – 0.71 mmol/L</i>	12.1 – 15.0 mg/dL <i>0.72 – 0.89 mmol/L</i>	> 15.0 mg/dL > 0.89 mmol/L
URINALYSIS <i>Standard International Units are listed in italics</i>				
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h <i>0.200 – 0.999 g/d</i>	1,000 – 1,999 mg/24 h <i>1.000 – 1.999 g/d</i>	2,000 – 3,500 mg/24 h <i>2.000 – 3.500 g/d</i>	> 3,500 mg/24 h > 3.500 g/d
Pediatric > 3 mo - < 10 years	201 – 499 mg/m ² /24 h <i>0.201 – 0.499 g/d</i>	500 – 799 mg/m ² /24 h <i>0.500 – 0.799 g/d</i>	800 – 1,000 mg/m ² /24 h <i>0.800 – 1.000 g/d</i>	> 1,000 mg/ m ² /24 h > 1.000 g/d

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

Section Appendix 11-2
Addendum 1 – The Female Genital Grading Table for Use in Microbicide Studies

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
GENERAL					
Odor	No complaint	Mild-moderate unpleasant odor	Severe unpleasant odor	NA	NA
PAIN AND TENDERNESS (Specify Area: Vulvar/Perineum, Vagina, Cervix (including cervical motion tenderness), Uterus, Adnexae, Pelvic/Lower Abdominal, or Ovulatory)					
*Note – if both pain and tenderness are present, only report the one with the most severe grade					
Pain* ¹	None	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities or the need for non-narcotic medication	Pain causing inability to perform usual social & functional activities or the need for narcotic medication	Disabling pain causing inability to perform basic self-care functions OR hospitalization (other than emergency room visit) indicated
Tenderness* ¹	None	Mild tenderness	Moderate tenderness	Severe tenderness	NA
Dyspareunia (pain with sexual activity)	None	Pain causing no or minimal interference with sexual function	Pain causing greater than minimal interference with sexual function	NA	NA
Dysmenorrhea/cramping with menses	None	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities or the need for non-narcotic medication	Pain causing inability to perform usual social or functional activities or the need for narcotic medication	NA

¹ If pain or tenderness is included in the grading of another category (e.g., PID), it should not be graded again in the pain or tenderness category.

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Genital Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
GENITOURINARY SIGNS/SYMPTOMS – VULVA					
Vulvar/vaginal itching	None	Itching causing no, mild, or moderate interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities; may require intervention such as antihistamine or bathing to provide relief	NA	NA
Vulvar edema	None	Mild, non-pitting edema	Moderate, 1-2+ pitting edema	3+ pitting edema, severe enough to require urinary drainage, or weeping edema ± skin breakdown	NA
Vulvar erythema	None	Erythema covering < 50% of vulvar surface	Erythema covering ≥ 50% of vulvar surface	NA	NA
Vulvar lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules - no treatment indicated	Blisters, ulcerations or pustules, with treatment indicated	Severe epithelial disruption with hospitalization indicated	NA
Vulvar rash	None	Rash covering < 50% of vulvar surface	Rash covering ≥ 50% of vulvar surface	Severe epithelial disruption with hospitalization indicated	NA
Bartholin's or Skene's gland	No findings	Cyst with no inflammation	Cyst or abscess with outpatient intervention indicated	Cyst or abscess with hospitalization indicated	Necrotizing fasciitis from Bartholin's abscess
GENITOURINARY SIGNS/SYMPTOMS – VAGINA					
** Note – if vaginal discharge is present both by history and on examination, only report the one with the most severe grade					
Vaginal edema	None	Mild-moderate engorgement	Loss of ruggae and friability	NA	NA
Vaginal erythema	None	Erythema covering < 50% of vaginal surface	Erythema covering ≥ 50% of vaginal surface	NA	NA

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Genital Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Vaginal dryness	No complaint	Dryness causing no or minimal interference with usual sexual, social, & functional activities	Dryness causing greater than minimal interference with usual sexual, social, & functional activities	NA	NA
Vaginal discharge by participant report **	Participant's usual amount of discharge, regardless of color or quantity	Mild-moderate increase in amount above participant baseline - no sanitary protection required	Profuse increase in discharge requiring pad use or other hygienic intervention	NA	NA
Vaginal discharge as observed by clinician ** (red or brown discharge should be reported under bleeding, not discharge)	Slight amount of discharge, any color	Mild-moderate increase in amount	Significant increase in amount with pooling in vagina on examination	NA	NA
Vaginal abrasions or lacerations (including probable applicator injuries)	None	Superficial disruptions and disruptions extending through the mucosa with minimal impact on life	Large disruptions extending through the mucosa or large superficial disruptions, hospitalization not indicated	Large disruptions extending through the mucosa or large superficial disruptions, hospitalization indicated	Lacerations extending into the peritoneal cavity, bladder, or rectum
Vaginal lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules, no treatment indicated	Blisters, ulcerations, or pustules with treatment indicated	Severe epithelial disruption requiring hospitalization	NA
Vaginal and Cervical masses (polyps, myomas, or possible malignancy)	None or normal variants such as Nabothian cyst or Gartner duct cyst	Polyp or myoma or undiagnosed mass without symptoms	Polyp, myoma, or undiagnosed mass causing mild symptoms, e.g., bleeding/pain not requiring more than mild analgesia	Polyp, myoma, or undiagnosed mass causing severe symptoms, e.g., bleeding/pain affecting bladder and bowel function	Visible cervical cancer
GENITOURINARY SIGNS/SYMPTOMS – CERVIX					
Cervical edema and friability	None	Edema without friability	Friable cervix	NA	NA

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Genital Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Cervical erythema	None	Erythema covering < 50% of cervix	Erythema covering ≥ 50% of cervix	NA	NA
Cervical discharge	White or clear discharge	Small amount of purulent discharge at os	Purulent discharge extending onto cervix or vagina	NA	NA
Visible cervical lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules, no treatment indicated	Blisters, ulcerations, or pustules with treatment indicated	NA	NA
GENITOURINARY SIGNS/SYMPTOMS – UTERUS					
Uterine masses/enlargement based on bimanual examination	Normal to 8 week size, no palpable myomas	Enlarged uterus and mild symptoms, e.g., bleeding/pain requiring mild analgesics	Enlarged uterus/myoma with moderate pain or symptoms, e.g., bleeding	Mass causing severe bleeding/pain or with impact on bowel/bladder function	Uterine mass that requires transfusion or surgery
Polyp, submucosal fibroid, or thickened endometrium detected by transvaginal ultrasound (new or increasing in size from prior exam)	None or unchanged/reduced in size from prior exam	New myomas < 6 cm diameter (single or multiple) or diameter increased < 6 cm since prior exam	New myomas ≥ 6 cm diameter (single or multiple) or diameter increased ≥ 6 cm since prior exam	Hospitalization and/or surgery indicated	NA
GENITOURINARY SIGNS/SYMPTOMS – ADNEXA					
Not pregnancy- or infection-related adnexal masses based on bimanual exam (use if no ultrasound done; if ultrasound done, use ultrasound categories below)	None, ≤ 4 cm, normal size ovary	> 4 cm with minimal or no symptoms	> 4 cm with severe symptoms, e.g., pain, but hospitalization not indicated (see footnote #1)	> 4 cm with severe symptoms, e.g., pain and hospitalization indicated (see footnote #1)	NA
Hydrosalpinx based on ultrasound	None	Asymptomatic, suspected hydrosalpinx	Hydrosalpinx with pain, but without evidence of infection or ectopic pregnancy	Signs/symptoms of infection with hospitalization and/or surgery indicated	NA
Adnexal mass based on ultrasound	None	Simple cyst, asymptomatic	Simple cyst, symptomatic	Mass suspicious for malignancy	Malignant mass

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Genital Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

INDIVIDUAL SIGNS/SYMPTOMS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
GENITOURINARY SIGNS/SYMPTOMS – ABDOMEN					
Abdominal mass not palpable on pelvic exam of unknown diagnosis	None or known (pre-existing) mass unchanged in size	New mass or increased size of known mass requiring mild analgesia with minimal impact	New mass or increased size of known mass with moderate symptoms	Mass causing severe bleeding/pain with impact on bladder/bowel function or with hospitalization indicated	Malignancy
GENITOURINARY SIGNS/SYMPTOMS – URINARY TRACT					
Urinary frequency	None	Up to 2 times participant's normal frequency	> 2 times participant's normal frequency	NA	NA
Dysuria	None	Superficial only	Deep ± superficial	Inability to void due to pain	NA
Hematuria	None	Microscopic, no intervention indicated (beyond evaluation for infection)	Gross blood in urine or medical intervention/evaluation indicated (beyond evaluation for infection)	Persistent bleeding with transfusion, hospitalization or intervention indicated to obtain hemostasis (endoscopy, interventional radiology, or operative)	Profuse hemorrhage with shock or orthostatic dizziness

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Genital Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

COMPOSITE SIGNS/SYMPTOMS (Use instead of individual categories if 2 or more signs/symptoms are present)					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD (Use if all signs/ symptoms would individually be Grade 0 or 1)	GRADE 2 MODERATE (Use if one or more signs/symptoms would individually be Grade 2 and all others Grade 0 or 1)	GRADE 3 SEVERE (Use if one or more signs/symptoms would individually be Grade 3)	GRADE 4 POTENTIALLY LIFE- THREATENING
NO ORGANISM IDENTIFIED BUT INADEQUATE TESTING PERFORMED					
Vulvovaginitis (combinations of pain, itching, erythema, edema, rash, tenderness, or discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
Cervicitis (combinations of dyspareunia, erythema, edema, tenderness, and discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
PID (if Gonorrhea or Chlamydia identified use that category)	None	NA	Cervicitis with mild uterine tenderness, ± mild cervical motion tenderness, no signs of peritoneal irritation	More diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution
NO ORGANISM IDENTIFIED AFTER APPROPRIATE TESTING PERFORMED					
Vulvovaginitis (combinations of pain, itching, erythema, edema, rash, tenderness, or discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
Cervicitis (combinations of dyspareunia, erythema, edema, tenderness, and discharge)	None	Mild signs/ symptoms	Moderate signs/ symptoms	Severe signs/ symptoms	NA
PID (if Gonorrhea or Chlamydia identified use that category)	None	NA	Cervicitis with mild uterine tenderness, ± mild cervical motion tenderness, no signs of peritoneal irritation	More diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Genital Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

INFECTIONS AND DYSPLASIA					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
GENITOURINARY INFECTIONS					
Genital herpes	No lesions	Characteristic ulcerative or vesicular lesions confirmed by culture, PCR, Tzanck prep or other diagnostic test of lesion or previous type-specific serology, covering < 25% of vulva, vagina, or cervix	Same criteria as mild but covering 25-50% of vulvar, vaginal, or cervical surface	Same criteria as mild but covering > 50% of vulvar, vaginal, or cervical surface	Symptoms of significant systemic involvement, e.g., encephalitis, hepatitis
Candida	Absence of symptoms regardless of candida test results	Positive culture, wet mount, or other laboratory test for yeast, with mild symptoms	Positive culture, wet mount, or other laboratory test for yeast, with moderate to severe symptoms	NA	NA
Trichomonas	Negative	NA	Positive wet mount, culture, PCR or other licensed test, excluding pap smear, showing T. vaginalis, regardless of symptoms	NA	NA
Bacterial Vaginosis (BV)	Negative	Asymptomatic BV diagnosed by Amsel criteria, wet mount, Gram stain, or licensed diagnostic test	Symptomatic confirmed by wet mount, Gram stain, or any licensed diagnostic test	NA	NA

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Genital Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

INFECTIONS AND DYSPLASIA					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Chlamydia	Negative	NA	Positive culture or other diagnostic test for Chlamydia, asymptomatic or with mild uterine or cervical motion tenderness (no signs of peritoneal irritation)	Positive test for Chlamydia with abdominal or uterine or adnexal tenderness on examination, with or without adnexal mass, diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution
Gonorrhea	Negative	NA	Positive culture or other diagnostic test for Gonorrhea, asymptomatic or with mild uterine or cervical motion tenderness (no signs of peritoneal irritation)	Positive test for Gonorrhea with abdominal or uterine or adnexal tenderness on examination, with or without adnexal mass, diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution or disseminated gonococcal infection
Urinary tract infection (by urinalysis and urine culture)	Negative	5-10 WBC/hpf on urinalysis with a negative culture per protocol definition (with or without symptoms)	> 10 WBC/hpf on urinalysis OR a positive culture per protocol definition (with or without symptoms)	Pyelonephritis	Sepsis (septicemia) due to urinary tract infection

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Genital Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

INFECTIONS AND DYSPLASIA					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Syphilis	Negative treponemal or non-treponemal test or both positive with known treatment and stable titers (< 4 fold increase)	NA	Syphilis diagnosed by a positive treponemal test along with a positive non-treponemal test and no previous treatment or a four-fold rise in titer on the non-treponemal test after previous treatment regardless of symptoms or non-oral lesions positive by darkfield exam for treponemes	Criteria for Grade 2 Syphilis in the presence of neurologic symptoms or a positive CSF VDRL or FTA-ABS	NA
GENITAL DYSPLASIA					
Condyloma (specify site: cervical, vaginal, vulvar, perianal)	None	Condylomata causing no or mild interference with daily function	Condylomata causing moderate interference with daily function	Condylomata causing severe interference with daily function, secondary infection, or hospitalization indicated	NA
Intraepithelial Neoplasia by biopsy (VIN, CIN, VAIN)	None	Intraepithelial Neoplasia 1 (IN1)	Intraepithelial Neoplasia 2 (IN2)	Carcinoma in situ (CIS)	Invasive carcinoma
Pap (use this category <u>only</u> if treatment performed without diagnostic testing, otherwise use biopsy category above)	nl PAP	ASCUS or LSIL	HSIL	Carcinoma in situ or Carcinoma	NA

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Genital Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
ABNORMAL UTERINE BLEEDING UNRELATED TO PREGNANCY					
Menorrhagia ² (prolonged and/or heavy menstrual bleeding)	Participant report of normal bleeding relative to her baseline	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Metrorrhagia ² (intermenstrual or frequent bleeding)	None or any expected nonmenstrual bleeding	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Unexplained infrequent bleeding (excludes expected absence of menses due to hormonal contraception or pregnancy/postpartum)	Participant report of normal or expected bleeding frequency	No menses for 1-3 months (missed menses)	No menses for > 3 months (oligomenorrhea/ amenorrhea)	NA	NA
Postcoital bleeding	None	Occasional (< 25% of coital acts) OR Increase from usual with no or minimal interference with usual social functioning (including sexual functioning)	Frequent (25-75% of coital acts) OR Increase from usual with moderate interference with usual social functioning (including sexual)	Consistent (> 75% of coital acts) OR Incapacitating or severe interference with usual social functioning (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock

² If both Menorrhagia and Metrorrhagia are present, a single adverse event should be reported as "Menometrorrhagia" and graded per the Menorrhagia grading scale.

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
COMPLICATIONS OF PREGNANCY					
First trimester bleeding	None	Spotting or bleeding less than menses with continuation of pregnancy	Bleeding like menses or heavier with continuation of pregnancy	Spontaneous abortion, or profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Spontaneous abortion with profuse bleeding and/or shock
Postabortal endometritis/salpingitis	None	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, requiring \leq 3 days of parenteral antibiotics	Severe symptoms requiring > 3 days of IV antibiotics or development of tubo-ovarian abscess	Ruptured TOA or diffuse peritonitis or severe uterine infection for which operative intervention indicated
Postpartum hemorrhage	EBL < 500 cc for vaginal delivery or < 1000 cc after CS or reported as normal	EBL 500-1000 for vaginal delivery or 1000-1500 for CS or reported as slightly increased	EBL > 1000 for vaginal delivery or > 1500 for CS, with or without mild dizziness, no transfusion required	Hemorrhage at a level for which transfusion of 1-2 units of packed cells, but no other blood products indicated	Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated
Postpartum endometritis	None	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, treated by \leq 3 days of parenteral antibiotics	Severe symptoms treated with > 3 days of IV antibiotics or addition of heparin	Severe infection or infection for which operative intervention is indicated
Chorioamnionitis	None	Fever (38°C – 38.4°C or 100.4°F – 100.9°F) with two or more: FHR > 160 BPM, maternal HR > 120, uterine tenderness between contractions or purulent AF or preterm labor	Same as Grade 1 plus fever 38.5°C – 40°C or 101°F – 104°F	Criteria for Grade 2 plus fetal distress or fever > 40°C or 104°F	Criteria for Grade 3 plus either fetal demise or maternal symptoms of shock

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF
ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER 2004**

**Addendum 1
Female Genital Grading Table for Use in Microbicide Studies**

UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Episiotomy infection	None	Mild erythema, edema, and tenderness of wound	Fever > 38°C or 100.4°F with erythema, edema, and tenderness of wound	Fever with wound dehiscence or debridement required	Fever with signs of wound infection and shock or necrotizing fasciitis
Second/third trimester bleeding	None	Bleeding less than menses	Bleeding like menses or greater, but not requiring intervention	Bleeding requiring delivery or other intervention, e.g., transfusion	Bleeding with fetal demise or coagulopathy
Preterm rupture of membranes	None	NA	Preterm rupture with hospitalization but not resulting in delivery at less than 37 weeks' gestation	Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight	Delivery < 33 weeks' gestation or ≤ 1500 grams birth weight
Preterm contractions	None	Preterm contractions which resolve without medical intervention	Preterm contractions with cervical change which result in medical intervention but not resulting in preterm delivery	Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight	Delivery < 33 weeks' gestation or ≤ 1500 grams birth weight
Poor fetal growth	At or above 10th percentile	Fetal growth < 10th percentile but ≥ 3rd percentile for gestational age by ultrasound or newborn exam	NA	Fetal growth < 3rd percentile for gestational age by ultrasound or newborn exam	NA

NOTE: For protocols utilizing this Addendum, when the same parameter appears in both this Female Grading Table and the main DAIDS AE Grading Table, use the grading scheme in this table.

Section Appendix 11-3
MTN 004 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

Per the MTN 004 protocol, the roles and responsibilities of the MTN 004 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports (protocol Section 8). Once the SDMC begins receiving study follow-up safety data, the PSRT will convene via regularly scheduled conference calls every two weeks. The frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT. Should any safety concerns be identified by the PSRT, these will be referred to the MTN Study Monitoring Committee (SMC) and/or DAIDS Vaccine and Prevention Data and Safety Monitoring Board (DSMB), as appropriate.
2. Respond to Investigator queries regarding temporary or permanent discontinuation of product use (protocol Section 9). The protocol specifies a limited number of situations in which study participants must discontinue product use; Investigators will implement these discontinuations in the absence of consultation with the PSRT. In other situations, however, discontinuation of product must be undertaken in consultation with the PSRT. These situations involve participants who:
 - (a) experience an AE that meets criteria for expedited reporting to DAIDS that is judged possibly related to product use;
 - (b) are unable or unwilling to comply with required study procedures; or
 - (c) otherwise might be put at undue risk to their safety and well-being by continuing product use.
3. Respond to Investigator queries regarding product resumption following occurrence of an AE judged probably or definitely related to study product that meets criteria for expedited reporting
4. Respond to Investigator queries regarding study eligibility and general AE management and reporting
5. Respond to Investigator requests for participant withdrawal from the study
6. Respond to Investigator requests for participant unblinding. There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. However, if an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator may notify the PSRT to consider and rule upon the request.

PSRT Composition

The following individuals currently comprise the MTN 004 PSRT:

- Ian McGowan, Protocol Chair, PSRT Chair
- Kailazarid Gomez, MTN CORE Clinical Research Manager
- Nancy Connolly, MTN Protocol Safety Physician
- Katherine Bunge, MTN Protocol Safety Physician
- Ross Cranston, MTN Protocol Safety Physician
- Mala S Shah, MTN Protocol Specialist
- Missy Cianciola, MTN SDMC Project Manager
- Yevgeny Grigoriev, MTN SDMC Clinical Affairs Research Nurse
- Barbra Richardson, MTN SDMC Co-Principal Investigator
- Alain Kouda, DAIDS Clinical Operations Coordinator
- Jeanna Piper, DAIDS Medical Officer
- Bill Kapogiannis, NICHD Health Science Administrator
- Patrician Emmanuel, Investigator of Record, University of South Florida
- Irma Febo, Investigator of Record, University of Puerto Rico
- Beatrice Chen, Investigator of Record, University of Pittsburgh

Ideally all of the above-listed PSRT members will take part in routine PSRT conference calls. At a minimum, the DAIDS and NICHD Medical Officers and one MTN Safety Physician must take part in all calls. If these three members are not present, the call may be deferred until the next scheduled call time unless a PSRT member requests a more immediate call.

MTN CORE Clinical Research Managers, SDMC Project Managers, and SDMC Statistical Research Associates may attend PSRT calls as observers and/or discussants.

Routine Safety Data Summary Reports: Content, Format and Frequency

The SDMC will generate and distribute standard safety data reports to the PSRT via e-mail one week prior to each scheduled PSRT conference call. Tabulations will be generated for all study participants combined (i.e., across all treatment groups) and will include:

- Listings of new AEs by body system (using MedDRA terms), severity, and relationship to study product
- A cumulative listing of all SAEs and EAEs reported to date
- A cumulative listing of all AEs reported to date as probably or definitely related to study product by body system and severity
- A cumulative listing of all grade 2, grade 3, and grade 4 AEs reported to date by body system and relationship to study product

During PSRT conference calls, the DAIDS Medical Officer or an MTN Protocol Safety Physician will summarize any additional EAE Forms received at the DAIDS Safety Office after the cut-off date for the SDMC data summary.

PSRT Communications

An email alias (mtn004psrt@mtnstopshiv.org) will be used to facilitate communication with the PSRT. All safety data summary reports from the SDMC will be distributed via this alias. A standard PSRT query form (below) will be used to elicit sufficient information to allow the PSRT to respond to each query. To ensure a timely PSRT response, one of the MTN Protocol Safety Physicians is responsible for providing a final response to the query or a request for more information from the study site (via email) within three business days after receipt of the query. All members of the PSRT are encouraged to review the information provided by the site and to offer their advice; however final determination rests with the PSRT Chair or Alternate Chair.

MTN 004 Protocol Safety Review Team Query Form, page 1 of 2

Instructions: Email completed form to rdc27@pitt.edu, kbunge@mail.magee.edu and nancycsc@gmail.com.

IMPORTANT: Complete all required fields so the PSRT has all information needed to respond to your query.

Site:
Completed by:

Query Date (dd-MMM-yy):
Email address:

PTID:
Enrollment Date (dd-MMM-yy):

Participant Age (in years):

- Reason for query:**
- Product use consultation:
 - Should use of study gel be temporarily discontinued (held)?
 - Should use of study gel be permanently discontinued (held)?
 - Should use of study gel be resumed?
 - Request for consultation on AE management
 - Request to withdraw participant from the study
 - Request to unblind participant's gel assignment
 - Other, specify:

Is this query a request for the PSRT to consult on an adverse event (AE)?

- Yes → continue completing this page
- No → skip to Comments on page 2

Primary AE of concern:

AE onset date (dd-MMM-yy):

AE severity grade at onset:

Relatedness to study gel:

- Definitely related
- Probably related
- Possibly related
- Probably not related
- Definitely not related

Current study gel administration:

- No change
- On hold
- Permanently discontinued
- Not applicable

Has this AE been reported on a SCHARP AE Log form?

- Yes
- No

Has this AE been reported as an EAE?

- Yes
- No

Has this AE been assessed more than once?

- Yes
- No → skip to Comments on page 2

Date of most recent assessment (dd-MMM-yy):

Status of AE at most recent assessment:

- Continuing, stabilized (severity grade unchanged)
- Continuing, improving → severity grade decreased to
- Continuing, worsening → severity grade increased to
- Resolved

MTN 004 Protocol Safety Review Team Query Form, page 2 of 2

Comments: Provide additional details relevant to this query. If gel use has been held, include date of last reported gel application prior to the hold (per participant report).

End of Form for Site Staff. Email completed form to the MTN 004 MTN Protocol Safety Physicians rdc27@pitt.edu, kbunge@mail.magee.edu and nancycsc@gmail.com. If an email response is not received from the PSRT within 3 business days, re-contact the MTN Protocol Safety Physicians and/or the MTN CORE (kgomez@fhi.org, or llevy@fhi.org) for assistance.

FOR PSRT USE ONLY — PROVIDE RESPONSE TO QUERY HERE

PSRT Responding Member:

PSRT Response Date (dd-MMM-yy):

Query Outcome:

- Approved
- Not approved
- Not applicable

PSRT Comments:

Section Appendix 11-4

MTN 004

SERIOUS ADVERSE EVENT (SAE) REPORT FORM

Protocol Number	Centre	Country	Subject Number							

Date of Report: ___/___/___
(DD) (MMM) (YYYY)

<p>1. TYPE OF REPORT</p> <p><input type="checkbox"/> Initial Report</p> <p><input type="checkbox"/> Follow-Up Report (#___)</p> <p><input type="checkbox"/> Final Report</p>	<p>2. DEMOGRAPHICS</p> <p>PTID: _____</p> <p>Date of Birth: ___/___/___ (DD) (MMM) (YYYY)</p> <p>RACE: <i>Please circle one</i></p> <p>American Indian or Alaskan Native</p> <p>Asian</p> <p>Black or African American</p> <p>Native Hawaiian or Other Pacific Islander</p> <p>White</p> <p>Mixed</p> <p>Other-Specify _____</p>
<p>3. SERIOUS ADVERSE EVENT</p> <p><i>Please provide diagnosis (or signs or symptoms if diagnosis not known)</i></p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>	<p>4. START DATE of EVENT</p> <p>___/___/___ TIME: ___:___ hr (DD) (MMM) (YYYY)</p> <p>STOP DATE of EVENT</p> <p>___/___/___ TIME: ___:___ hr (DD) (MMM) (YYYY)</p> <p>("--" if ongoing)</p>

Section Appendix 11-4

MTN 004

SERIOUS ADVERSE EVENT (SAE) REPORT FORM

Protocol Number	Centre	Country	Subject Number							

<p>5. CRITERIA FOR SAE or REPORT</p> <p><i>Please specify the criteria for considering this as a SAE, and mark all that apply</i></p> <p><input type="checkbox"/> Resulted in Death</p> <p> Was an autopsy performed <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p> If Yes, please provide report</p> <p><input type="checkbox"/> Life Threatening Event</p> <p><input type="checkbox"/> Resulted in Persistent of Significant Disability/Incapacity</p> <p><input type="checkbox"/> Required or Prolonged Hospitalisation</p> <p> Admission Date ___ / ___ / ___</p> <p> (DD) (MMM) (YYYY)</p> <p> Discharge Date ___ / ___ / ___</p> <p> (DD) (MMM) (YYYY)</p> <p><input type="checkbox"/> Congenital Anomaly/Birth Defect</p> <p><input type="checkbox"/> Medically Significant</p> <p><input type="checkbox"/> Pregnancy</p> <p><input type="checkbox"/> Cancer (IND studies only)</p> <p><input type="checkbox"/> Other (specify) _____</p>	<p>6. SEVERITY</p> <p><input type="checkbox"/> Mild/ Grade 1</p> <p><input type="checkbox"/> Moderate/ Grade 2</p> <p><input type="checkbox"/> Severe/ Grade 3</p> <p><input type="checkbox"/> Life Threatening/ Grade 4</p>
	<p>7. OUTCOME</p> <p><input type="checkbox"/> Recovered</p> <p><input type="checkbox"/> Recovered with sequelae</p> <p><input type="checkbox"/> Ongoing at study conclusion</p> <p><input type="checkbox"/> Died</p> <p><input type="checkbox"/> Unknown</p>
	<p>8. RELATIONSHIP OF EVENT TO STUDY PRODUCT</p> <p><input type="checkbox"/> Definitely</p> <p><input type="checkbox"/> Probably</p> <p><input type="checkbox"/> Possibly</p> <p><input type="checkbox"/> Probably not</p> <p><input type="checkbox"/> Not Related</p>

Section Appendix 11-4
MTN 004

SERIOUS ADVERSE EVENT (SAE) REPORT FORM

Protocol Number	Centre	Country	Subject Number							

<p>9. ACTION TAKEN WITH STUDY PRODUCT(S)</p> <p><input type="checkbox"/> None</p> <p><input type="checkbox"/> Study Product(s) administration delayed</p> <p><input type="checkbox"/> Study Product(s) administration stopped</p> <p><input type="checkbox"/> Not Applicable</p>	
<p>10. REOCCURENCE OF EVENT AFTER FURTHER ADMINISTRATION STUDY PRODUCT(S)</p> <p><input type="checkbox"/> No Recurrence of Event</p> <p><input type="checkbox"/> Event Reappeared</p> <p><input type="checkbox"/> Unknown at time report</p> <p><input type="checkbox"/> Not Applicable</p>	<p>11. WAS THE SUBJECT WITHDRAWN FROM STUDY DUE TO THIS EVENT?</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p>

12. STUDY PRODUCT(S) INFORMATION

Study Product Name Study Product	Dose Form & Strength	Route/Site	Start Date
(DD/MMM/YYYY)			
_____	_____	_____	___/___/___
___/___/___			
_____	_____	_____	___/___/___
___/___/___			
_____	_____	_____	___/___/___
___/___/___			
Indication: _____			
Blinding Broken: <input type="checkbox"/> Yes			
<input type="checkbox"/> No			
<input type="checkbox"/> Not Applicable			

13. CONCOMITANT MEDICATIONS. A photocopy of the Concomitant Medications CRF page may be attached

Section Appendix 11-4

MTN 004

SERIOUS ADVERSE EVENT (SAE) REPORT FORM

Protocol Number	Centre	Country	Subject Number							

Drug Name	Strength	Dose	Frequency	Route	Reason for Use	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY) or Continuing
<i>Example: Panadol</i>	<i>500mg</i>	<i>2 tabs</i>	<i>4 hourly</i>	<i>Oral</i>	<i>Headache</i>	<i>01/NOV/2004</i>	<i>01/NOV/2004</i>

14. MEDICATIONS USED TO TREAT SAE

Drug Name	Strength	Dose	Frequency	Route	Reason for Use	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY) or Continuing
<i>Example: Panadol</i>	<i>500mg</i>	<i>2 tabs</i>	<i>4 hourly</i>	<i>Oral</i>	<i>Headache</i>	<i>01/NOV/2004</i>	<i>01/NOV/2004</i>

15. RELEVANT MEDICAL HISTORY. Please provide details of past and/or current medical history that may have contributed to this SAE (including allergies)

16. DESCRIPTION OF EVENT. Please provide brief narrative description of SAE, including relevant diagnostic findings, lab data, treatment etc.

Section Appendix 11-4

MTN 004

SERIOUS ADVERSE EVENT (SAE) REPORT FORM

Protocol Number	Centre	Country	Subject Number							

17. SIGNATURES.

Investigators Name: _____ Date: _____
(DD/MMM/YYYY)

Investigators Signature: _____

Starpharma Clinical Representative Name: _____ Starpharma Receipt
Date: _____
(DD/MMM/YYYY):

Starpharma Clinical Representative Signature: _____

18. STARPHARMA REVIEW

COMMENTS:

19. MEDICAL MONITOR EVENT CLASSIFICATION:

a) Is the event RELATED to the study product use?

Yes

No

If no, please
comment: _____

b) Is the event UNEXPECTED?

Yes

No

If unexpected, which criteria is the event to be identified in the Investigator Brochure by?

Section Appendix 11-4

MTN 004

SERIOUS ADVERSE EVENT (SAE) REPORT FORM

Protocol Number	Centre	Country	Subject Number							

- Nature
- Severity
- Frequency

20. REGULATORY REPORTING REQUIREMENTS:

- Is the event reportable to Local and Worldwide Regulatory Authorities (Related to Study Product)? Yes No
- Reportable due to Unexpected and Life Threatening (Report within 7 days) Yes No
- Reportable due to Unexpected and Non Life Threatening (Report within 15 days) Yes No

Regulatory Reports Sent To:

- Australia Yes No Sent By: _____ Date Sent; _____
- Europe Yes No Sent By: _____ Date Sent; _____
- USA Yes No Sent By: _____ Date Sent; _____

21. MEDICAL MONITOR SIGNATURE:

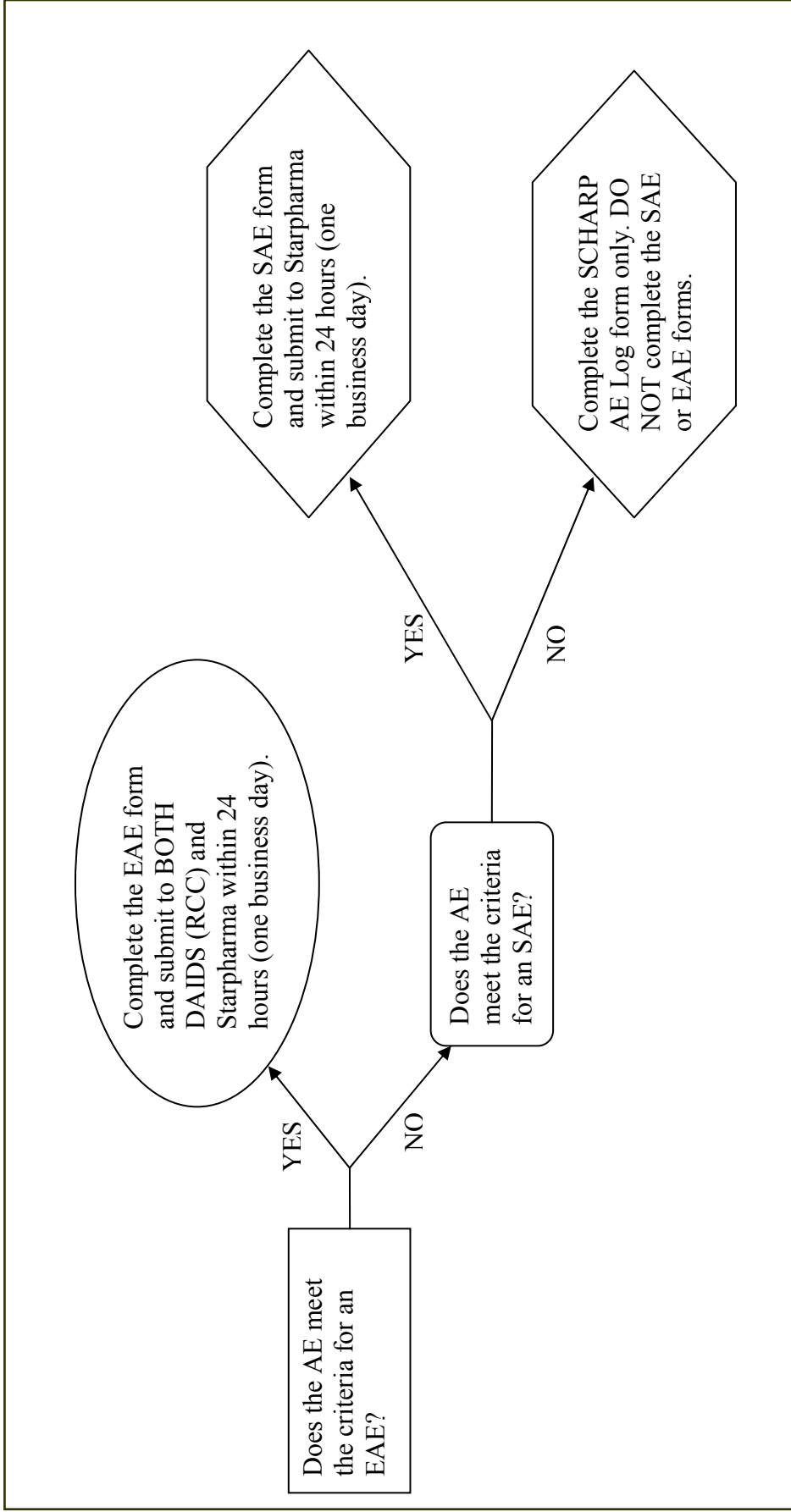
Medical Monitor Name: _____ Date and Time: _____

_____ (DD/MMM/YYYY)

(00:00hr)

Medical Monitor Signature: _____

Section Appendix 11-5
MTN 004 EAE/SAE Reporting Requirements



Section Appendix 11-6
MTN004 Safety Phone, Expedited Review, and Product Hold Procedures

Clinical Affairs Safety Associates (CASAs) may be alerted to events meeting expedited AE review/study product hold criteria, via a phone call from a study site, email communication from a study site, and/or pause rule alert/report produced by SCHARP reports programmers.

For each event, regardless of the notification method, CASAs are responsible for verifying the event, determining whether this event meets the expedited AE review/study product hold criteria, and taking appropriate action.

Resources for Event Review

The following resources will be used when reviewing the event:

- Study Protocol
- Female Genital Toxicity Table and DAIDS Toxicity Table
- DataFax
- Clinical information provided by the site

CASA Actions upon Alert Notification

When alerted of an event, the CASA undertakes the following action steps:

Verify the event

Confirm the severity grade—verify that the grading is appropriately described based on the:

Female Genital Grading Table for clinical events

and/or

DAIDS Toxicity Table for laboratory events.

In all cases, the CASA must check the description, value and calculation for accurate grading.

Confirm the relatedness of the event to the study product - Regardless of which kind of event occurs, the CASA checks the AE plate for relatedness or obtains this information from the site. The CASA must also verify that the site PI is involved in determining relatedness.

Request further information from the site as needed.

Determine that the event meets AE review/study product hold criteria

Determine if the event meets expedited AE review/study product hold criteria, and which rule it meets.

For an event that DOES meet expedited AE review/study product hold criteria

Request that study site staff send an e-mail summary of the event to SCHARP Clinical Affairs (CA).

Request that study site staff promptly fax supporting case report forms (CRFs) to SCHARP DataFax at 206.667.4805.

Section Appendix 11-6
MTN004 Safety Phone, Expedited Review, and Product Hold Procedures

For MTN004 the following CRFs may be faxed for supporting documentation:

- Safety Lab Results (SL-1 and SL-2)
- Pelvic Laboratory Results (PLR-1)
- Follow-up Genital Symptoms (FGS-1)
- Follow-up Pelvic Exam (FPE-1 through FPE-3)
- AE Logs (AE-1)
- Genital Bleeding Assessment (GBA-1 through GBA-3)

Request that SCHARP Data Operations staff promptly validate the new plates in the database (e-mail sc.dcsups.org).

Prepare a safety history, using the DataFax Safety History Tool.

For an event that does NOT meet expedited AE review/study product hold criteria

Communicate the event to MTN Safety Physicians and Clinical Affairs staff via sc.clin.aff@scharp.org describing the event and indicating why the event does not meet the pause rules.

Determine that the event requires a study product hold

If the SCHARP Safety Associate determines that the criteria for an accrual pause and study-wide product hold are met (see above for criteria), the SCHARP Safety Associate contacts one of the MTN Safety Physicians by telephone as soon as possible to convey the details of the safety events.

Contacting the PSRT

If the Safety Physician confirms that the events may warrant an accrual pause and product hold (regardless of whether or not they meet the protocol criteria), the SCHARP Safety Associate notifies the DAIDS Medical Officer, NICHD Medical Officer, and Protocol Chair (by phone if possible).

Expedited PSRT Review

The SCHARP Safety Associate convenes an expedited PSRT review by conference call so that the PSRT can review all relevant safety information. At minimum, the PSRT quorum, consisting of the DAIDS Medical Officer, NICHD Medical Officer, and an MTN Safety Physician, are required to convene the PSRT review call. Per protocol, the PSRT makes the final decision on whether or not to pause study accrual and hold study product for all participants in the study.

Notify Clinical Sites of the Study Product hold

If the PSRT decides to pause study accrual and hold study product for all participants, the CASA notifies FHI via telephone that a study product hold has been initiated. FHI is responsible for promptly notifying the site PI

Section Appendix 11-6
MTN004 Safety Phone, Expedited Review, and Product Hold Procedures

or designee at all sites. FHI will send out an official study notification e-mail to the entire protocol team.

Contacting the Participants

Staff at each site is responsible for contacting each participant currently using study product at their site. They will instruct these participants to immediately and permanently discontinue study product use and return to the study site as soon as possible to return all unused study product in their possession. Site staff must make every effort to contact each participant personally in order to confirm that she has received and understood instructions to permanently discontinue study product use. Site staff will continue to complete regular study visits for participants in active follow-up. However, sites must immediately discontinue study screening and enrollment activities.

Document the outcome of the expedited AE review/study product hold

Promptly document and disseminate the outcome of the expedited AE review/study product hold.

AE Review

No communication with the site is required if the PSRT's decision is to carry on with the trial with no modifications to the protocol.

If the PSRT's decision is to initiate a study product hold, refer to information above for specific activities

Study Product Hold

FHI sends an e-mail regarding the outcome of the PSRT discussion to all those who received notification of the pause. This e-mail will include further information as to the continuation of the study.

Section 12. Laboratory Considerations

12.1 Overview and General Guidance

This section contains information on the laboratory procedures performed in MTN 004.

As transmission of HIV and other infectious agents can occur through contact with contaminated needles, blood, blood products, and vaginal secretions, all study staff must take appropriate precautions when collecting and handling biological specimens. Sites must have appropriate written safety procedures in place before study initiation. Guidance on universal precautions available from the US Centers for Disease Control and Prevention can be found at the following websites:

- http://www.cdc.gov/ncidod/dhqp/bp_universal_precautions.html

Some laboratory procedures will be performed in study site clinics or laboratories and others in the MTN Network Laboratory (NL) in Pittsburgh, PA. Serum SPL7013 levels will be done at Starpharma Ltd Bioanalytical Laboratory in Melbourne, Australia. Table 12-1 lists for each test the testing location, specimen type, specimen container and kit/method (if specified). Table 12-2 specifies blood collection by visit type and suggested volumes.

Regardless of whether tests are performed in clinic or laboratory settings, study staff that performs the tests must be trained in proper associated QC procedures prior to performing the tests for study purposes; training documentation should be available for inspection at any time.

The Pittsburgh site was added in June of 2009; some modifications will be noted in the rest of this section for this site because shipping is not required to get specimens to the MTN Network Laboratory.

Table 12-1
Overview of Laboratory Testing Locations, Specimens,
and Methods for MTN 004

Test	Testing Location	Specimen Type	Tube/Container	Kit/Method
Urinalysis* (dipstick)	In clinic	Urine	Plastic screw top cup	Bayer Multistix 9 or Uristix 4
Urine pregnancy test	In clinic	Urine	Plastic screw top cup	Quidel Quick Vue
Urine SDA for	MTN Network	Urine	Plastic screw	BD Probetec/

gonorrhea and Chlamydia	Lab		top cup	GenProbe Aptima
HIV antibody screen	Clinic/Local Lab	Plasma or whole blood (<i>serum acceptable</i>)	Lavender (EDTA) or red (no additive) top tube	FDA approved test
Complete blood count	Local Lab	Whole Blood	Lavender top tube	Not specified
Liver function panel	Local Lab	Serum	Red or marble (serum separator) top	Not specified
Creatinine	Local Lab	Serum	Red or marble top	Not specified
Coagulation panel	Local Lab	Plasma	Blue (sodium citrate) top tube	Not specified
Pap Smear	Local Lab	Ecto- and Endocervical cells	Slides	Not specified
Vaginal pH	In clinic	N/A	N/A	S/P pH Indicator Strips
Vaginal wet preparation	In clinic	Vaginal fluid swab	N/A	N/A
Gram-stained vaginal smear	MTN Network Lab	Vaginal fluid Swab	Slides	Network Lab procedure
Quantitative vaginal culture	MTN Network Lab	Vaginal swab	Port-a-Cul transport tubes by BD	Network Lab procedure
Cervical cytokine panel	MTN Network Lab	Cervical Swab	2 Swabs → cryovials w PBS	Luminex 100™
RPR	Local Lab	Serum or Plasma	Red or lavender tube	Not specified
Herpes culture	Local Lab	Ulcer Swab	Viral Transport Media (Must be appropriate for HSV-2)	Not specified
Serum SPL7013 level	Starpharma	Plasma	Green (Lithium Heparin) tubes	Capillary Electrophoresis

*Perform Urine Culture and Sensitivity as clinically indicated per local SOP

Sites are responsible to ensure that specimen volumes do not exceed what is described in the informed consent process. The MTN NL may request details of collection containers and volumes for this purpose.

**Table 12-2
Scheduled Blood Collection by Visit Type and Suggested Volumes**

Visit Type	Total Blood Volume (ml)	Volume By Tube Type (ml)	Purpose
Screening 1 Visit	15	Red Top:5	Liver and Kidney Tests, Syphilis Test
		Purple Top:5	Hematology, HIV-1 Antibody Test
		Blue Top:5	Coagulation
Enrollment	25	Red Top:5	Liver and Kidney Tests
		Purple Top:5	Hematology, Plasma Archive
		Blue Top:5	Coagulation
		Green Top:10	SPL7013 Level
One Week Visit	15	Red Top:5	Liver and Kidney Tests
		Purple Top:5	Hematology
		Blue Top:5	Coagulation
Two Week Visit	25	Red Top:5	Liver and Kidney Tests
		Purple Top:5	Hematology, Plasma Archive
		Blue Top:5	Coagulation
		Green Top:10	SPL7013 Level

Notes: Additional blood may be collected for any clinically indicated testing. Red top tubes contain no additive. Lavender top tubes contain EDTA. Blue top tubes contain sodium citrate. Green tops contain Lithium Heparin.

Ideally, one method, type of test kit, and/or combination of test kits will be used for each protocol specified test throughout the duration of the study. If for any reason a new or alternative method or kit must be used after study initiation, site laboratory staff must perform a validation study of the new method or test prior to changing methods. The MTN NL must be notified before the change and can provide further guidance on validation requirements. Similarly, contact the MTN NL in cases of changes to normal ranges.

Provided in the remainder of this section is information intended to standardize laboratory procedures across sites. Adherence to the specifications of this section is essential to ensure that primary and secondary endpoint data derived from laboratory testing will be considered acceptable to all regulatory authorities across study sites.

12.2 Specimen Labeling

All containers into which specimens are initially collected (e.g., urine collection cups, blood collection tubes) will be labeled with SCHARP-provided Participant ID (PTID) labels. The date the specimens are collected should also be included on the label. If the date is handwritten, it should be in indelible ink (such as a Sharpie pen).

Microscope slides used for evaluation of vaginal/cervical fluids also will be labeled with SCHARP provided PTID labels. PTIDs are pre-printed on these labels; however study staff must write the specimen collection date on each label. The visit code also may be written on the label. (The Pittsburgh site may label the slides with Pencil and place SCHARP label on the slide holder).

When specimens are tested at the local lab, any additional labeling required for on-site specimen management and chain of custody will be performed in accordance with site SOPs. The following specimens will be entered into LDMS and labeled with LDMS-generated labels: stored plasma specimens, cervical swabs for cytokines, vaginal fluid slides prepared for Gram stain evaluation, vaginal cultures and SLP 7013 levels. These specimens will be shipped to the MTN NL or Starpharma for testing. (The Pittsburgh site will not use LDMS for gram stains, vaginal cultures and cervical cytokines.)

12.3 Procedures for Specimens that can not be evaluated

Specimens will be redrawn or recollected if it is found that they can not be evaluated per site SOP's. Sites will monitor specimen management problems as part of ongoing Quality Assurance. In cases where additional specimens need to be recollected either due to a laboratory error (lost or broken specimen or clerical error) or clinic error (clerical error), a protocol event form will be required.

12.4 Use of LDMS

The Laboratory Data and Management System (LDMS) is a program used for the storage and shipping of laboratory specimens. It is supported by the Frontier Science Foundation (FSTRF). LDMS must be used at all sites to track the collection, storage, and shipment of five types of specimens in MTN 004: plasma archive, cervical swabs for cytokines, vaginal cultures, vaginal fluids (air-dried on microscope slides for Gram stain evaluation), plasma SLP 7013 levels and returned applicators. (The Pittsburgh site will not use LDMS for gram stains, vaginal cultures and cervical cytokines.)

Detailed instructions for use of LDMS are provided at: <https://www.fstrf.org/ldms> (may require a password).

All sites will be required to maintain the current version of LDMS and monitor updates relating to use of the LDMS. It is crucial to be aware of proper label formats to ensure that specimens are correctly labeled. Sites will be responsible to back up their LDMS

data (frequency determined by site) locally and to export their data to FSTRF (at least weekly).

Questions related to use of LDMS in MTN 004 may be directed to Edward Livant or LDMS Technical (User) Support. Usual business hours for LDMS User Support are 7:30 am - 6:00 pm (ET) on Monday and Fridays and 7:30 am - 8:00 pm (ET) on Tuesdays, Wednesdays, and Thursdays. During business hours, please contact LDMS User Support as follows:

Email: ldmshelp@fstrf.org

Phone: +716-834-0900, ext 7311

Fax: +716-898-7711

LDMS User Support can be paged via email during off business hours if you are locked out of LDMS or experience errors that prevent you from completing LDMS lab work. To page LDMS User Support, email LDMS pager 1, 2 or 3 (addresses shown in Table 3 below) and include the following information in the body of your email:

- LDMS lab number (this is a three-digit number that is different from your network assigned clinical site number)
- The full telephone number at which you can be reached, including the country code and city code if you are outside the United States
- A short description of the problem

FSTRF no longer supports the use of pagers. The email addresses in Table 12-3 can still be used as needed.

Table 12-3
LDMS User Support Email Paging Details

Pager	Email Address
LDMS 1	ldmspager1@fstrf.org
LDMS 2	ldmspager2@fstrf.org
LDMS 3	ldmspager3@fstrf.org

Each site must export its LDMS data to Frontier Science (FSTRF) on a weekly basis. Exported data are used by the MTN SDMC to generate a monthly specimen repository report and to reconcile data entered in LDMS with data entered on study case report forms. Any discrepancies identified during the reconciliation are included in a monthly discrepancy report for each site. Sites are expected to resolve all discrepancies within two weeks of receipt of the report. The MTN NL is responsible for reminding sites to adhere to the two week timeframe and for following up with sites that do not resolve discrepancies within two weeks. The MTN SDMC reviews the discrepancy reports for critical samples (e.g., plasma needed for confirmatory HIV testing) that appear to be missing, and works with the NL and site staff to undertake appropriate corrective action. All corrective action should be documented in paper-based clinic and/or laboratory records as appropriate, and entered in the details section of LDMS. The NL and SDMC

will discuss and document any items that, although resolved, appear 'irresolvable' in LDMS.

**Table 12-4
LDMS Specimen Management Guide to Logging in 004 Specimens**

The table below should be used as a guide when logging in 004 specimens. Please use the LDMS codes listed below when logging in specimens for each test listed. Tests that are listed as local do not require that a sample be logged into the LDMS. See Appendix 12-1 for a copy of the LDMS tracking sheet.

Test	Primary	Additive	Derivative	Sub Add/Derv	Primary Volume	Aliquot Volume	Units
Vaginal Swab for Culture to NL	VAG	PAC	SWB	N/A	1	1	N/A
Cervical Swab for Cytokines	CXS	PBS	CXS	N/A	1	1	N/A
Vaginal Swab for Gram stain to NL	VAG	NON	SLD	GRS	1	1	N/A
Plasma for storage	BLD	EDT	PL 1/2	N/A	2 to10	0.5	ml
SPL7013 level to Starpharma	BLD	HEP	PL 1/2	N/A	10	2.5	ml

**Table 12-5
Specimen Shipping Summary**

Specimen	Use LDMS?	Ship to:	Shipping schedule
Vaginal Swab for Culture to NL	Yes*	MTN Network Lab	Must be shipped overnight
Cervical Swab for Cytokines	Yes*	MTN Network Lab	Batched until end of study
Vaginal Swab for Gram stain to NL	Yes*	MTN Network Lab	Ship at the same time as cultures
Plasma for storage	Yes	MTN Network Lab	Store at site until notified by MTN
SPL7013 level	Yes	Starpharma	Batched until end of study
Urine for GC/CT testing	No	MTN Network Lab	1-2 times per week

*Except Pittsburgh

12.5 Urine Testing for Pregnancy, Urinary Tract Infection, Chlamydia, and Gonorrhea

The urine tests performed at each study visit will depend on the time point of the visit and the clinical presentation of the participant. In general, at study visits when urine testing is required, a single specimen will be collected and then aliquotted for each test when possible. When doing multiple tests from one specimen, the correct order is separation of urine for the Chlamydia and Gonorrhea first, pregnancy test next, then the urine dipstick last.

Note: Testing for Chlamydia and Gonorrhea is done at screening and when clinically indicated only. Viva gel interferes with the BD Probetec so post enrollment GC/CT testing will be performed on the Gen Probe Aptima. See below for details.

12.5.1 Specimen Collection

- The participant should not have urinated within one hour prior to urine collection.
- Provide the participant with a sterile, plastic, preservative-free screw-top urine collection cup labeled with a SCHARP-provided PTID label.
- Instruct the participant not to clean the labia prior to specimen collection.
- Collect the first 15-60 ml of voided urine in a sterile collection cup. (Not mid-stream).
- Instruct the participant to screw the lid tightly onto the cup after collection.
- At visits when pregnancy testing and/or dipstick urinalysis is required, aliquot 5-10 ml for these tests and store the remaining urine at 2-8° C or introduce the urine immediately into the UPT for subsequent chlamydia and gonorrhea testing.

12.5.2 Pregnancy Testing

At visits when pregnancy testing is required, aliquot approximately 5-10 ml of urine from the specimen collection cup and pipette from this aliquot for pregnancy testing. If the supernatant is too dark to read the pregnancy test, another urine sample will need to be collected.

Note: Protocol-specified pregnancy testing is not discontinued during pregnancy.

The Quidel QuickVue One-Step hCG urine pregnancy test must be used at all sites. This test was selected for use in MTN 004 because of its ease of use and the validity of test results in the presence of the study gels. Perform the test according to site SOPs and the package insert. Do not perform any other urine pregnancy tests for confirmatory purposes.

Pregnancy status is a critical participant safety consideration in MTN 004. All sites must maintain an adequate inventory of the QuickVue One-Step test kits at all times. Inventory should be monitored closely and re-supply orders placed at least 8-12 weeks in advance of actual need (or longer if needed per site procurement policies and procedures). The date and time of pregnancy testing must be documented.

12.5.3 Dipstick Urinalysis

Dip the urinalysis test strip into an aliquot of urine. At visits when both pregnancy testing and dipstick urinalysis are required, the same aliquot should be used for both tests, but the urinalysis should be performed after urine has been pipetted from the aliquot for the pregnancy test.

Bayer/Siemens urine test strips must be used at all sites. Perform this test according to site SOPs and the package insert. Assess and record results for glucose, protein, leukocytes and nitrites. If leukocytes or nitrites are positive, perform a urine microscopy and a urine culture according to local SOP. To avoid overgrowth of bacteria, refrigerate specimen before and during transport to laboratory.

Inventory should be monitored closely and re-supply orders placed at least 8-12 weeks in advance of actual need (or longer if needed per site procurement policies and procedures). Notify the NL immediately if any kit inventory or quality control problems are identified, so that appropriate action can be taken.

12.5.4 Chlamydia and Gonorrhea Testing

Note: Testing for Chlamydia and Gonorrhea is done at screening and when clinically indicated only. Viva gel interferes with the BD Probetec so post enrollment GC/CT testing will be performed on the Gen Probe Aptima. The only change for collection and transport procedures will be the transport tube used. In cases where GC/CT testing is indicated at follow up, follow these instructions but use the alternate transport tube.

This testing will be done at the MTN NL using the BD Probe Tec Method. Sites will be required to send samples in using the BD Urine Preservation Tubes (UPT). Following are shipping instructions:

Instructions for transferring urine into the UPT

- Collect urine as noted above.
- Open the UPT kit and remove the UPT and transfer pipette. Label the UPT with the participants PTID number and date.
- Hold the UPT upright and firmly tap the bottom of the tube on a flat surface to dislodge any large drops from inside the cap.
- Uncap the UPT and use the transfer pipette to transfer enough urine to fill the tube to the level indicated on the tube between the black lines. Do not under fill or overfill the tube.
- Cap tightly and invert the tube 3-4 times to ensure that the specimen and reagent are mixed.
- The specimen can now remain at 2-30°C for 30 days.

Shipping instructions for urine samples to Magee-Women's Research Institute

(If vaginal cultures are being shipped on the same day combine the specimens in one shipping container. See shipping instructions for vaginal specimens section 12.7.5)

- Urine specimens are stable for 30 days therefore specimens can be batched and sent once a week if your turn around time is 8-9 days.
- Fill out a shipping manifest with the information listed in the example located in appendix 12-2 (Do not use LDMS for urine specimens).
- Package the specimens according to the IATA packing instructions 650 for non-refrigerated specimens.
 - Place the tubes in a biohazard zip-lock bag.
 - Enclose the tubes in the small Styrofoam container without ice packs.
 - Place the Styrofoam container inside the cardboard box.
 - Insert the box and the shipping manifest in a FedEx Diagnostic envelope.
 - Check 2 day delivery on the FedEx air bill when shipping only urines (2 day delivery will save shipping costs)
- The day of shipment, send Lorna Rabe an e-mail at rsilkr@mwri.magee.edu with the FedEx tracking number.

If sending Monday through Thursday, send to:

Lorna Rabe

Magee-Womens Research Institute

204 Craft Ave, Room 530

Pittsburgh, PA 15213

Phone # 412-641-6042

(If sending on Friday, do not check Saturday delivery)

12.6 Blood Testing for HIV, Syphilis, Hematology, Liver, Renal Function, and Plasma Archive and Plasma SPL7013 Levels

The blood tests performed at each study visit vary depending on the time point of the visit and potentially the clinical presentation of the participant. Perform all tests according to site SOPs and package inserts.

12.6.1 Specimen Collection and Initial Processing

Label all required tubes with a SCHARP-provided PTID label at the time of collection.

After collection:

- Allow red top tubes (no additive) or marble top (serum separator tubes) to clot, then centrifuge per site SOPs to yield serum for syphilis, liver function, and renal function testing.
- Lavender top tubes (additive = EDTA) should be gently inverted at least eight times after specimen collection to prevent clotting. EDTA tubes are used for hematology, HIV testing and plasma archive. If whole blood for hematology testing and plasma are to be taken from the same tube, the hematology must be completed before the tube is centrifuged and aliquotted. If whole blood is to be used for multiple tests, ensure that the tube is well mixed before removing any specimen.

- Blue top tubes (additive=sodium citrate) should be gently inverted at least eight times after specimen collection to prevent clotting. They are then centrifuged per site SOP's for coagulation testing. NCCLS recommends using 3.2% sodium citrate.
- Green top tubes (additive=lithium heparin) should be inverted at least eight times after collection to prevent clotting. These are used for SPL7013 levels. The specimens are placed immediately after collection into an ice water bath (slurry) and centrifuged as soon as possible after collection (\leq 1hour).

Note: If locally available tube top colors do not correspond with the tube additives specified above, use appropriate tubes based on the additives, not the listed tube top colors.

12.6.2 HIV Testing

Plasma (whole blood and serum are also acceptable) will be tested for HIV using tests that have been validated at the study site per the Clinical Laboratory Improvement Amendment (CLIA) standards. All tests, and associated QC procedures, must be documented on local laboratory log sheets or other laboratory source documents.

At all sites, HIV infection status at screening will be assessed using an FDA-approved enzyme immunoassay (EIA) per the MTN 004 HIV testing algorithm (see appendix III in the current version of the MTN 004 protocol). If the EIA is non-reactive, the participant will be considered HIV-uninfected. If the EIA is reactive, an FDA-approved Western Blot (WB) will be performed; if additional blood must be drawn for the WB, this is still considered sample 1 per the algorithm. If the WB is negative, the participant will be considered HIV-uninfected; this situation is not anticipated-contact the MTN NL if this occurs. If the WB is positive, the participant will be considered HIV-infected. A second specimen will be drawn for confirmatory testing. If the WB is indeterminate, the participant will be asked to present to the study site in approximately one month for re-testing. At that time, the EIA will be repeated and the above-described algorithm will be followed. A WB will only be performed if the EIA is reactive.

Kit inventories should be monitored closely and re-supply orders placed at least 8-12 weeks in advance of actual need (or longer if needed per site procurement policies and procedures). Notify the NL immediately if any kit inventory or quality control problems are identified, so that appropriate action can be taken.

At all sites, all test results must be documented on local laboratory log sheets or other laboratory source documents. In addition to initialing or signing the testing logs to document review and verification of the results, the second staff member must also record the time at which the results were reviewed and verified.

12.6.3 Syphilis Testing

Syphilis testing will be performed using a rapid plasma reagin (RPR) screening test followed by a confirmatory microhemagglutinin assay for *Treponema pallidum* (MHA-TP) or *Treponema pallidum* haemagglutination assay (TPHA). Any RPR, MHA-TP, and/TPHA test may be used at each study site; however titers must be obtained and reported for all positive RPR tests. RPR tests may be performed on either serum or plasma. MHA-TP and TPHA tests must be performed on serum. All testing and QC procedures must be performed and documented in accordance with study site SOPs. For reactive RPR tests observed during screening, a confirmatory test result must be received and appropriate clinical management action taken, prior to enrollment in the study. Clinical management should include repeat RPR tests at quarterly intervals following syphilis diagnosis to confirm treatment effectiveness. If the RPR titer does not decrease fourfold or revert to sero-negative within three months after treatment, treatment should be repeated.

Please consult the MTN NL with any questions related to Syphilis testing to confirm treatment effectiveness and/or interpretation of unusual test results.

Questions related to result interpretation vis-à-vis eligibility and enrollment in the study should be directed to the MTN 004 Protocol Safety Review Team.

12.6.4 Hematology Testing

Complete blood counts with five-part differentials will be performed at all sites. Each of the following must be analyzed and reported:

- Hemoglobin
- Hematocrit
- Platelets
- White blood cell count with differential
- Red blood cell count

These tests will be performed on EDTA whole blood.

12.6.5 Liver and Renal Function Testing

The following tests will be performed to evaluate liver and renal function:

Liver Function

- Aspartate aminotransferase (AST)
- Alanine transaminase (ALT)

Renal Function

- Creatinine

These chemistry tests will be performed on serum.

12.6.6 Coagulation Panel

The following tests will be performed to evaluate coagulation function:

- Activated Partial Thromboplastin Time
- International Normalized Ratio (calculated from Prothrombin Time)

Coagulation tests will be performed on Sodium Citrate Plasma.

12.6.7 SPL7013 Plasma Levels

The lithium heparin specimens are placed immediately after collection into an ice water bath (slurry) and centrifuged as soon as possible after collection (≤ 1 hour). The whole blood will be centrifuged at 3000 rpm (approximately $1000\times g$) for 10 minutes. If red blood cells are not sufficiently separated from plasma, centrifugation for a further 5 minutes may be required. The plasma will be transferred into two approximately equal portions (approximately 2.5ml each) and placed in labeled 5ml polypropylene tubes and frozen at approximately -20°C .

Samples will be assayed for SPL7013 levels using a validated capillary electrophoresis bioanalytical method at the Starpharma Pty Ltd bioanalytical laboratory, Melbourne, Australia. The samples will be stored on site during the study and then shipped directly from the sites to Starpharma in Australia. At the end of the study, one set of samples should be shipped and the other retained until advised by the MTN leadership group. The MTN NL will communicate with the sites to help coordinate the shipment with Starpharma.

The shipping address is:

Starpharma Pty Ltd Bioanalytical Laboratory
Baker Building
75 Commercial Road
Melbourne, 3004, VIC Australia.

Samples will be shipped in a sufficient amount of dry-ice to keep the plasma frozen for transport. A separate SOP from Starpharma will be provided to the sites with more detailed instructions.

12.6.8 Plasma Archive

EDTA plasma will be archived from enrollment and week 2 visits. These will be stored at -70°C and batched until the end of the study.

- LDMS will be used to label and track the specimens.
- Within 24 hours of collection, process the blood for plasma according to site SOP's.
- Prepare as many 0.5 ml aliquots as available to store. If less than one 0.5 ml aliquot is available, store that plasma and inform the MTN NL for instruction.
- At the end of the study, the MTN NL will contact the sites with instructions for shipping.

- Note: plasma archive is only applicable if participant consents to long term storage.

12.7 Testing of Vaginal and Cervical Specimens

Refer to the Screening and Follow-up Pelvic Exam checklists in other sections of this manual for further information of the required sequence of specimen collection and diagnostic procedures to be performed during study pelvic exams.

12.7.1 Vaginal pH

Vaginal pH will be assessed as part of on-site evaluations for bacterial vaginosis. S/P pH Indicator Strips (pH range 3.6 to 6.1) provided by MTN NL must be used at all sites, as follows:

- During pelvic examination vaginal fluids are collected via swab on the vaginal walls and then swabbed onto the pH strip. Avoid collecting the swab from the cervix and the pooled secretions in the fornix which have a higher pH.
- Match the resulting color of the indicator strip to the color scale provided with the strips to determine the pH value.
- Record the pH value directly onto the appropriate case report form. It is not necessary to record pH values onto laboratory log sheets or other source documents prior to recording values onto case report forms.

12.7.2 Vaginal Fluid Wet Mount Testing

Wet mount procedures for this study consist of two different preparations —saline prep and potassium hydroxide (KOH) prep —for diagnosis of bacterial vaginosis, trichomoniasis, and candidiasis, as summarized in Table 12-4.

If wet prep slides are read in-clinic by clinical staff, results may be recorded directly onto appropriate case report forms. If slides are read by lab staff (either in the local laboratory or a designated in-clinic lab area), results must be recorded onto laboratory log sheets or other laboratory source documents and then transcribed onto appropriate case report form.

Prior to study initiation, the MTN NL will conduct on-site training and proficiency testing for clinic and laboratory staff designated to perform wet mounts. CLIA regulations require semi-annual proficiency testing; therefore the MTN NL will administer a web-based proficiency testing approximately every six months. The MTN NL will post wet mount slides on the MTN web pages for this purpose every 6 months; results will be entered directly on the website (contact: Lorna Rabe: rsilkr@mwri.magee.edu). The MTN NL will report results back to the Laboratory Manager and also specify any corrective action that may be needed based on the results. Contact the MTN NL for additional information and guidance on performing and documenting the proficiency testing. Also contact the MTN NL when new laboratory staff is hired, so that appropriate training can take place prior to such staff performing wet mounts for study purposes.

**Table 12-6
Summary of Wet Prep Assessments and Diagnostic Criteria**

Assessment	Saline Prep	KOH Prep
Whiff Test	Not applicable	Positive if fishy amine odor detected
Clue Cells	Individual cells rather than clusters of cells should be examined. Positive if at least 20% clue cells observed. Cells must be completely covered with bacteria (<i>Gardnerella vaginalis</i> and/or anaerobic GNR) to be counted as clue cells.	Not applicable (clue cells are lysed by KOH)
Trichomonads	Positive if at least one motile trichomonad is observed. Actively motile organisms are easily seen upon low power (10X). High power (40X) may be needed to detect less vigorously motile organisms when only the flagella may be moving.	Not applicable (organisms are lysed by KOH)
Yeast	Positive if pseudohyphae and/or budding yeast are observed. Pseudohyphae and budding yeast may be obscured by epithelial cells. These cells will be lysed by KOH, thus pseudohyphae and budding yeast not observed in saline prep may be observed in KOH prep.	Positive if pseudohyphae or budding yeast are observed.

Note: Bacterial vaginosis will be diagnosed based on the presence of any three of the following Amsel's criteria: homogenous vaginal discharge, vaginal pH greater than 4.5, positive whiff test, at least 20% clue cells

Prepare and examine wet prep slides according to study site SOPs as follows:

- Use a pencil to write the PTID and specimen collection date on one side of the frosted end of two microscope slides. Affix a SCHARP-provided PTID label to the other side of the slides (on the frosted end, under the pencil markings) and write the specimen collection date in indelible ink (e.g. Sharpie pen) on each label.
- Immediately following collection from the lateral vaginal wall via swab, smear vaginal fluid specimens onto each slide. Alternatively, the swab may be placed in

a glass or plastic tube with approximately six drops (100 µL) sterile physiologic saline to allow for non-immediate slide preparation. In this case, vaginal fluid specimens should be smeared onto the two slides upon receipt from the collecting clinician.

- Apply one drop of 10% KOH to one slide and immediately perform whiff test for a “fishy” amine odor. Then apply cover slip.
- Apply one drop of sterile physiologic saline to the second slide, emulsify with the vaginal fluid specimen, and then apply coverslip. Examine immediately at 10X magnification for epithelial cells, motile trichomonads, budding yeast, and pseudohyphae. Examine at 40X magnification to determine whether observed epithelial cells are clue cells and quantitate the cells. Clue cells are irregularly bordered squamous epithelial cells that are completely covered with bacteria (*Gardnerella vaginalis*). Clue cells must comprise at least 20 percent of the observed epithelial cells in order for the saline prep to be considered positive for clue cells.
- Examine the KOH slide at both 10X and 40X magnification for yeast and pseudohyphae.

12.7.3 Vaginal Fluid Dried Smears for Gram Staining

In addition to the wet mounts described above, dried vaginal fluid smears will be prepared for Gram staining and assessment for bacterial vaginosis at the MTN NL. Two slides will be prepared at each required time point and both will be entered into LDMS. One will be shipped to the MTN NL and the other will be archived on site until written notification is received from the SDMC that the slide may be discarded. Instructions for slide preparation and shipping are provided below.

12.7.4 Slide Preparation and Storage

- Use a pencil to write the PTID and specimen collection date on one side of the frosted end of one microscope slide. Affix a SCHARP-provided PTID label to the other side of the slides (on the frosted end, under the pencil markings) and write the specimen collection date in indelible ink (e.g. Sharpie pen) on each label. Also write “V” for vaginal on each label.
- Immediately following specimen collection from the lateral vaginal wall via swab, roll the swab across each of the slide. (Be sure to collect the specimen from opposite the vaginal wall used for the wet mount specimen collection.) Do not place the swab in saline, transport medium, or any transport container prior to slide preparation.
- Allow the specimens to air-dry on the slides. Do not heat-fix.
- Deliver the slides and an LDMS Specimen Tracking Sheet to the local LDMS laboratory.
- Using the LDMS Tracking Sheet, log the slides into LDMS (specimen type = VAG) and label the slides with LDMS labels. Place the LDMS label on the frosted end of the slide, on the opposite side of the slide from the SCHARP-provided label, on top of the pencil markings.

- Place one slide in a plastic slide holder and send to the MTN NL at Magee with the vaginal swab for culture. (See shipping instructions below).
- The slide from the screening visit should be sent with the enrollment visit specimens.
- Store the second slide in the slide box location assigned in LDMS at room temperature. (This is a backup slide incase the first is lost or unreadable).
- Pittsburgh only: label the gram stain slide using pencil on the frosted site with the PTID, Date and Visit Code. Place a SCHARP sticker on the outside of the slide holder.

Note: The MTN 004 protocol requires that dried smears be prepared for all potential study participants at Screening, however all slides will not have Gram stains done at the MTN NL. Slides will only be assessed for participants who enroll in the study and, for enrolled participants who undergo more than one screening pelvic exam, only slides from the exam that confirmed eligibility will be assessed.

12.7.5 Vaginal Swab for Quantitative Culture

In addition to the wet mounts and Gram stains, vaginal swabs will be collected for Quantitative cultures and sent to the MTN NL. Shipping instructions follow.

- Collect the specimen for culture by rotating 2 Dacron swabs several times over the lateral wall of the vagina. Insert both swabs into 1 Port-A-Cul transport tube (labeled with a SCHARP label), submerging the swabs into the gel and breaking off the shafts of the swabs, and capping. (The Port-A-Cul transport tubes will be provided by MTN NL.)
- The specimen may be kept at controlled room temperature for up to 4 hours. It must be refrigerated after that and shipped with ice packs.
- Deliver the Port-A-Cul and the LDMS specimen tracking sheet to the local LDMS laboratory.
- Using the LDMS Tracking Sheet, log the specimen into LDMS (specimen type = VAG) and label the Port-A-Cul tube with LDMS labels.
- Use LDMS to generate a shipping manifest for the cultures to be shipped.
- Ship the Port-A-Cul tube and the vaginal smear for gram stain the same day of collection by overnight courier.
- Place the Port-A-Cul in a biohazard bag and secure in the leak-proof container with absorbent material. Place the container, ice packs, slides, and a copy of the manifest in a cardboard box lined with Styrofoam.
- Use diagnostics packing code 650, UN3373.
- Confirm the address is correct (see below). Because the Research Institute is not open for delivery on the weekend the specimens taken on Friday must be sent to the hospital address in order for delivery on Saturday.
- Pittsburgh only: label the port-a-cul with the SCHARP label. LDMS not required.

If sending Monday through Thursday Send to:
Lorna Rabe

Magee-Womens Research Institute
204 Craft Ave, Room 530
Pittsburgh, Pa. 15213
Phone# 412-641-6042

If sending on Friday for Saturday delivery, send to:

Lorna Rabe, C/O Safety and Security
Magee-Womens Hospital
300 Halket St.
Pittsburgh, Pa. 15213

Phone # 412 641-4191 (this is the Safety and Security #)

** Be sure to check Saturday delivery on the Fed Ex label

Notify the MTN NL via email when the shipment has been picked up from the site by the courier/shipping company. Attach an electronic copy of the shipping manifest to the email notification, and include the following information in the notification: name of courier/shipping company, shipment tracking number, number of boxes shipped, date of shipment, and expected date of arrival.

12.7.6 Cervical Sample for Cytokines Collection

Cervical swab for Cytokines

- Two Dacron swabs will be taken.
- Gently insert one Dacron swabs 1 cm into the cervical os and rotate 360 degrees to absorb the fluid.
- Place the swab in a cryovial with 400ul of PBS. Break off the end of the swab to allow closure of the cryovial and securely attach the cap. Attach a SCHARP-provided label to the vial.
- Repeat with the second Dacron swab as described above.
- Samples must be placed on dry ice and frozen at -70°C as soon as possible after collection.
- Deliver both cryovials and an LDMS Specimen Tracking Sheet to the local LDMS laboratory.
- Using the LDMS Tracking Sheet, log the cryovials into LDMS (specimen type=CXS) and generate an LDMS cryovial label for each tube. Affix the LDMS label to the cryovial (over the SCHARP-provided PTID label).
- Store the cryovial(s) in the freezer locations assigned in LDMS at -70°C.
- Specimens will be batched and shipped to the NL on dry ice at the end of the study.
- Pittsburgh only:
 - Label the cryovials with the SCHARP label. LDMS not required.
 - Dry Ice not required if the specimen is received at the lab within 60 minutes of collection.

12.7.7 Papanicolaou (Pap) Test

Pap smears will be performed at sites. At visits when Pap smears are required, ecto- and endocervical cells will be collected after all tissues have been visually inspected and all other required specimens have been collected. Specimen collection, slide preparation, slide interpretation, and QC procedures must be performed and documented in accordance with study site SOPs.

At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are not adequately sensitive and specific for STIs, Pap smear findings associated with STIs should not be considered diagnostic of any infections. Rather, such findings should be handled as follows:

- Do not consider STI-related notations on Pap smear result reports when assessing participant eligibility for the study. Use only the results of protocol specified STI tests for purposes of eligibility determination.
- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report.
- Provide treatment as needed based on the results of the protocol-specified tests.
- If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the participant's next study visit that takes place after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests.

12.7.8 HSV-2 Culture

When clinically indicated, HSV-2 culture will be performed. This testing should be done per local site standards. The specimens may be batched and tested at the end of the study unless results are needed for clinical management.

Appendix 12-1 LDMS Tracking Sheet

Participant ID <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="text-align: center;"> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> - <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> - <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> - <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <small>Site Number Protocol Participant Number Chk</small> </div> <div style="text-align: center;"> Visit Code (Vst) <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <small>dd</small> </div> <div style="text-align: center;"> Specimen Collection Date <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <input style="width: 20px; height: 20px; border: 1px solid black;" type="text"/> <small>dd MMM yy</small> </div> </div>			
# of TUBES (or Specimens)	PRIMARY SPECIMEN TYPE	ADDITIVE	INSTRUCTIONS FOR LAB <small>Unless otherwise noted, enter sub add/derivative code as N/A</small>
<input type="checkbox"/>	Blood (BLD)	EDT (purple top)	At the Enrollment and 2-Week Visits, lab to divide plasma into as many 0.5 mL aliquots as available to store for plasma archive. Store with derivative PL 1/2.
<input type="checkbox"/>	Blood (BLD)	HEP (green top)	At the Enrollment and 2-Week Visits, lab to divide plasma into (2) aliquots of approximately 2.5 mL each for SPL7013 level testing. Store with derivative PL 1/2.
<input type="checkbox"/>	Vaginal Gram Stain Slide (VAG)	NON (no additive)	Re-label with LDMS label. Store duplicate slides (one for on-site storage, and one for shipping and testing at MTN Central Lab). Store with derivative SLD and sub add/derivative GMS.
<input type="checkbox"/>	Cervical Swab (CXS)	PBS	Re-label cryovial with LDMS label. Store with derivative CXS.
<input type="checkbox"/>	Vaginal Swab (VAG)	PAC	Re-label cryovial with LDMS label. Store with derivative SWB.

Comments: _____

Initials: _____ **LDMS Data Entry Date:**

 / _____
Sending Staff Receiving Staff dd MMM yy LDMS Staff

Appendix 12-2: Sample Shipping Manifest

MTN 004

Site:

**Contact person: (fill in)
(Fill in address)**

Phone number:

Fax number:

E-mail address:

Shipment Date _____

Specimen type: Urine for GC/CT testing

PTID	Collection Date	Visit Code

Comments _____

Ship to:
Lorna Rabe Magee-Womens Research Institute 204 Craft Ave. Room 530 Pittsburgh, Pa. 15213 412-641-6041

**On the day of shipment E-mail the FedEx tracking # to
rabelk@upmc.edu and cosentinola@upmc.edu**

Section 13. Behavioral Measures

The Behavioral Measures of MTN-004 protocol will be collected via Web-based questionnaires. This procedure is a variation of the CASI (Computer Assisted Self-Interview), the only difference being that the data entered are not stored in the laptop but rather are transmitted instantly to a server selected by SCHARP (Statistical Center for HIV/AIDS Research and Prevention). Behavioral Measures will be the Baseline Behavioral Questionnaire, taken at the Enrollment Visit; the Acceptability and Adherence Questionnaire, taken at the Two-Week Clinic visit; and the Study Burden Questionnaire taken at the Three-Week Clinic Visit (see Table 1, below).

NOTE. No Web-based questionnaires are to be completed at the Week 1 Visit. The Adherence Assessment at Week 1 Visit is referring only to administration of the Adherence CRF at this visit.

Table 1: Timing of Behavioral Measures

Study Timeline	Behavioral Measures (Web-based Questionnaires)
Enrollment - Day 0	Baseline Behavioral Questionnaire
Week 2 (Day 14)	Acceptability and Adherence Questionnaire
Week 3 (Day 21)	Study Burden Questionnaire

The purpose of this SSP section is to assist you to set the equipment ready for the participant to respond to the Web-based Behavioral Measures.

13.1 GENERAL COMPUTER USE

Each study site will have a laptop connected to the Web for the participants to use. Sites should select a location for the laptop that is private (i.e. the screen should be out of sight of staff members or other participants while answers are being entered), but allows study staff to be nearby to answer questions or assess whether the participant is having computer problems. There should be an electrical outlet and a jack for broadband connection, unless a reliable wireless connection is used. The laptop should be plugged into an AC power source. An external mouse should be connected to the laptop. To minimize problems with laptops, keep the laptop plugged into a power source, avoid having food or drink nearby, and keep the area where the laptop is used clutter-free. You should have a virus program installed on your laptop. You may also check your computer for the most current dangerous viruses, worms and Trojans by downloading and running either (or both) of the following programs:

- 1) Stinger.exe from: <http://vil.nai.com/vil/STINGER/>;
- 2) Microsoft Windows Malicious Software Tool from: <http://www.microsoft.com/downloads/details.aspx?FamilyId=AD724AE0-E72D-4F54-9AB3-75B8EB148356&displaylang=en>.

We recommend having a back-up laptop or desktop available for your use, in the event that you cannot get your laptop to work.

Each site is responsible for addressing issues of security, privacy, background noise, lighting, ergonomics, and overall participant comfort in its site-specific procedures. Staff members should be familiar with the questionnaire in case participants raise any questions.

Refer to the operations manual of the PC or laptop you will use for hardware and software specifications, and instructions on how to use the computer (i.e., turning a computer on and off, etc.).

Please refer to Section 13.3 for guidelines and contact information regarding troubleshooting and problems with administering the questionnaire.

For questions regarding general computer problems, please refer to Section 13.3 in this manual for contact information.

Section 13.1.1 below gives instructions on Keyboards and Mouse Use.

13.1.1 Keyboard and Mouse Use

The laptop keyboard is like most standard computer keyboards in its function and use. An external mouse will be attached to the laptop to facilitate clicking on different areas of the Web page presented. The Logitech V200 Cordless Notebook Mouse specified for this protocol includes instructions on how to connect it. They are simple steps:

- Plug the receiver into the laptop's USB port.
- Install the batteries in the mouse by pressing the top, lower case of the mouse to release and lift the case.
- Install the software that came with the product.

To use the mouse, the following instructions are provided:

- To move the cursor, move mouse.
- To select an object, tap left button once.
- To select and move (or drag) an object, position the cursor on the object and double tap the left button, leaving your finger down the second time. Then move the selected object by sliding your mouse.
- To open an object, position the cursor on the object and then double tap the left button twice.
- To scroll up, down, left and right, use the tilt wheel. The wheel enables zooming in and out.

The difference between 'left clicking' and 'right clicking' is that left clicking selects the item while right clicking provides access to the pop-up menu. When not in use, attach the receiver to mouse for convenient storage. This turns the mouse off. To turn mouse on, remove the receiver from the base.

References in this SSP to 'clicking' on icons or other items displayed on the screen are meant to direct the user to press the left button. For problems or troubleshooting, refer to installation manual.

13.2 ADMINISTERING BEHAVIORAL QUESTIONNAIRES

Behavioral questionnaires will be administered three times during the course of the study:

- Enrollment Visit – Baseline Behavioral Questionnaire
- Two-Week Clinic Visit – Acceptability and Adherence questionnaire
- Three-Week Clinic Visit – Study Burden Questionnaire

If any participant discontinues trial participation early, she will be encouraged to respond to the Acceptability and Adherence Questionnaire and the Study Burden Questionnaire at the time she exits the study (early termination visit).

The following sections provide guidance on administering the questionnaires at each Visit

13.2.1 Baseline Behavioral Questionnaire (Enrollment Visit)

The Baseline Behavioral questionnaire will assess different types of sexual behavior (vaginal/anal/oral), condom use per act (with/without), partner gender (male/female), partner type (significant other/casual partner), and partner HIV status (positive, negative, unknown) in the recent past. It will also include questions on past use of vaginal hygiene products, medications, desiccants, douches, tampons, and vaginal pregnancy prevention methods. Participants will also be asked to report on substance use, and likelihood of using a microbicide in the future.

To begin, access to the Web page for the Baseline Behavioral Questionnaire at the following URLs:

- English Questionnaire - www.scharp.org/MTN004baseline
- Spanish Questionnaire - www.scharp.org/MTN004baseline/Spanish

Once the questionnaire is accessed, staff should complete the following:

- 1) Log in by entering the PTID and Study Code (MTN004)
- 2) Instruct the participant to follow the online instructions for using both the keyboard and mouse, as well as moving from page to page to answer questions (i.e., using the “Next” button).
Note: Initially, the participant will be presented with simple practice questions (e.g., “choose all that applies,” “indicate how many times,” “choose one of a fixed set of answers”).
- 3) Verify participant's comfort with using the mouse and keyboard, and navigating through the questionnaire.
- 4) Allow the participant to complete the practice questions, assisting her, if needed, to make sure she understands how to answer, and how to change invalid entries.
Note: Invalid entries are those that are not accepted by the program, either because they contradict information that the participant previously entered or because they are not permitted (e.g., numbers that are out of the possible range, like saying she used the gel 100 times).
- 5) Let the participant know that she can refuse to answer any question.
Note: If the participant is unsure of her answer, encourage the participant to make her best guess rather than refuse. Answer any questions that the participant may have and let the participant know that you are available for help or questions.
- 6) Once the practice has been successfully completed, ensure that the participant has read and understands the statement encouraging her to respond to all questions as truthfully as possible.
- 7) Instruct the participant to get you once she sees a message at the end of the questionnaire, indicating that she has completed the questionnaire.
- 8) Leave the room and allow the participant to proceed to the Baseline Behavioral Questionnaire and respond to the questionnaire on her own. The participant should be the only person in the room at the time she is completing the questionnaire.

13.2.2 Acceptability and Adherence Questionnaire (Two Week Clinic Visit)

At the Two-Week Clinic Visit, the participant will complete the Acceptability and Adherence Questionnaire. The Acceptability and Adherence Questionnaire will explore the experiences the participant had during the prior 14 days of study gel use, her likes and dislikes concerning the gel, the applicator, the application process, any changes she may have introduced or may wish to introduce in the volume used, any problems (e.g. leakage) she may have had, partner’s reaction,

sexual enjoyment, condom use during sexual intercourse using the gel, changes in her habitual sexual behavior, and likelihood of using a microbicide in the future.

To begin, access the Web page for the Acceptability and Adherence Questionnaire at the following URLs:

- English Questionnaire - www.scharp.org/MTN004accept.
- Spanish Questionnaire - www.scharp.org/MTN004accept/Spanish.

- 1) Log in by entering the PTID and Study Code (MTN004)
- 2) Instruct the participant to get you once she sees a message at the end of the questionnaire, indicating that she has completed the questionnaire.
- 3) Leave the room and allow the participant to proceed to the Acceptability and Adherence Questionnaire and respond to the questionnaire on her own. The participant should be the only person in the room at the time she is completing the questionnaire.

13.2.3 Study Burden Questionnaire (Three-Week Clinic Visit)

At the Three-Week Clinic Visit, the participant will complete the final Web-based survey, the Study Burden Questionnaire. This questionnaire will explore, through structured questions, the participant's overall experiences during the trial, and her likes and dislikes.

To begin, access the Web page for the Study Burden Questionnaire at the following URLs:

- English Questionnaire - www.scharp.org/MTN004burden.
- Spanish Questionnaire - www.scharp.org/MTN004burden/Spanish.

- 1) Log in by entering the PTID and Study Code (MTN004)
- 2) Instruct the participant to get you once she sees a message at the end of the questionnaire, indicating that she has completed the questionnaire.
- 3) Leave the room and allow the participant to proceed to the Study Burden Questionnaire and respond to the questionnaire on her own. The participant should be the only person in the room at the time she is completing the questionnaire.

Please refer to Section 13.3 below for guidelines and contact information regarding troubleshooting and problems with administering the questionnaire.

13.3 Troubleshooting and Contact Information

If you encounter any problems with the questionnaires, either accessing them or completing them, or with the laptop/desktop that you are using, notify the team by sending an email to the alias list mtn004webtroubleshoot@mtnstopshiv.org. A team of staff members (Ben Masse, Missy Cianciola, Jon Ringuette, and Julie Stofel at SCHARP; and Curtis Dolezal and Ana Ventuneac at the HIV Center) will be available to assist you to troubleshoot and resolve any problems you may have with the Behavioral Measures.

To facilitate the troubleshooting process, please indicate in your email a description of the problem, including a copy of error message(s), if any, and date and time of when the problem occurred. It will very useful to the MTN 004 Web Troubleshoot team to have an exact copy of error messages. To take a snapshot of an error message presented on the screen, simply maximize the screen containing the error message and hit Control (CTRL) and Print Screen (or PRT SC on most laptops) simultaneously on your

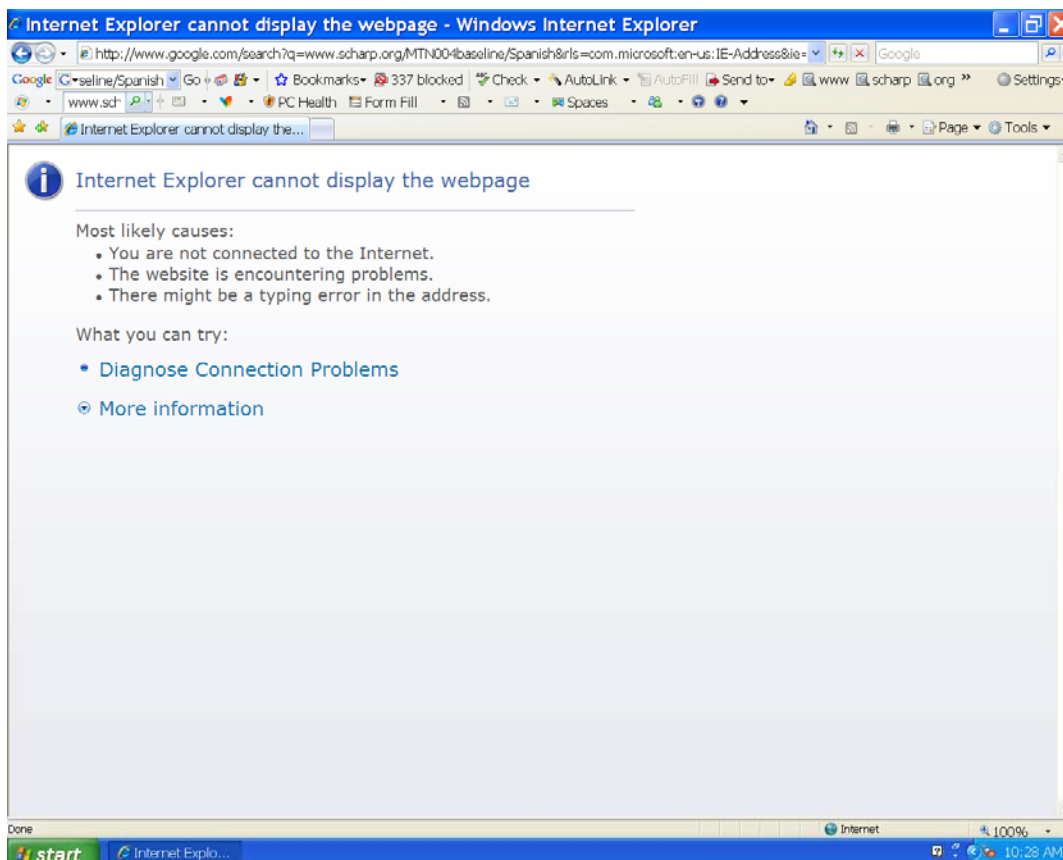
keyboard to create an image of your screen. Next, open Microsoft Word and paste your image (click on Edit and then Paste; or simply hit CTRL and V simultaneously). Save the Word file as MTN004WebProblem[insert date].doc and attach it to your email to the MTN 004 Web Troubleshoot team. Below is an example of an email message to the MTN 004 Web Troubleshoot team:

Email Message

To: **mtn004webtroubleshoot@mtnstopshiv.org**
From: XXX
Date: July 30, 2007, 10:28am EST
Re: MTN 004 Web Problem

No access to the Baseline Behavioral Questionnaire in Spanish (www.scharp.org/MTN004baseline/Spanish) on July 30, 2007 at 10:20am EST. A participant is expected in for a study visit at 11:00 am and will be ready to complete the questionnaire at 11:30am. HELP!

[Word document containing an image of the error message should be attached to the email (example of file: MTN004WebProblem_7-30-07.doc)]



Ana Ventuneac will coordinate efforts to quickly resolve any problems. She will keep a record of any problems in a log (MTN 004 Web Troubleshoot Log), track actions taken to correct problems, and inform

and follow up with team members, as appropriate. In case a problem occurs when the participant is at the site and actions to resolve the problem need to be taken immediately, you may contact:

- Ana Ventuneac at (212) 568-4352, (347) 432-0766, or ventune@pi.cpmc.columbia.edu

You may also contact:

- Missy Cianciola at 206 667-7290 or missy@scharp.org for questions about accessing the Web-based questionnaires
- SCHARP help desk at (206) 667-2822 or e-mail sc.helpdesk@scharp.org for any technical problems accessing the questionnaires

If a participant is answering the questionnaire and encounters a problem, exit the questionnaire by closing the browser page and then access the appropriate Web page again to log the participant in. The Web page with the question where a participant left off should be displayed. If the problem persists, contact mtn004webtroubleshoot@mtnstopshiv.org and call Ana Ventuneac so that actions can be taken immediately. The MTN 004 Web Troubleshoot team will assess the problem and communicate with you about resolutions. If the problem cannot be resolved quickly, an appointment should be made as soon as possible, preferably within a day or two, so that the participant can come back to complete the questionnaire. If this occurs, you should document it by keeping a record in the participant's file. A record will also be made in the MTN 004 Web Troubleshoot Log.

Refer to Appendix 13.1 for “Quick Tips for Web-Based Behavioral Measures”

Section Appendix 13-1

QUICK TIPS FOR WEB-BASED BEHAVIORAL MEASURES

- Prior to starting a questionnaire, make sure that the external mouse is connected and working properly. Determine whether the participant prefers to respond to the questionnaire in English or Spanish.
- Make sure that the participant is comfortable and has privacy to assure the confidentiality of her responses.
- Start the questionnaire by typing the Web address to the corresponding Behavioral Measure (NOTE: No Web-based questionnaires are to be completed at the Week 1 Visit.):
 1. Baseline Behavioral Questionnaire (Enrollment Visit)
 2. Acceptability and Adherence Questionnaire (Two-Week Clinic visit)
 3. Study Burden Questionnaire (Three-Week Clinic Visit)
- Make sure that the participant is comfortable with using the mouse and keyboard.
- Check to confirm that it is the correct questionnaire and that it is presented in the right language.
- Enter PTID, Study Code: MTN004, and enter PTID again to confirm.
- Allow participant to complete the practice questions.
- Assist the participant as needed.
- Instruct the participant that when she reaches the end of the survey, she will see a screen that says "Thanks, you have finished this questionnaire." The participant is not finished until she reaches this end screen. At that point the participant should leave the computer as is and inform the study coordinator. Exit the questionnaire by closing the browser screen.
- If, for any reason, the participant cannot complete the questionnaire, you may exit the questionnaire. If the participant is able to return to it, the questionnaire can be restarted by going back to the appropriate Web page and entering the PTID.
- If you encounter any problems with the questionnaires or with the laptop/desktop that you are using, notify mtn004webtroubleshoot@mtnstopshiv.org.

Section Appendix 13-2

BEHAVIORAL MEASURES - ENGLISH

Introduction

Section I: Baseline behavioral questionnaire

Table of Contents

Section:	Title:	Pages:
A	DEMOGRAPHICS	5-6
B	SEXUAL BEHAVIOR	7-13
C	VAGINAL & RECTAL DOUCHES, LUBRICANTS, AND OTHER PRODUCTS	14-15
D	LUBRICANT USE	16-18
E	SUBSTANCE USE & HIV TESTING	19-20
F	LIKELIHOOD OF USING MICROBICIDE	21
G	PLEASURE	22-23

PROGRAMMER: TEXT IN CAPITAL LETTERS SHOULD NOT BE PRESENTED TO THE PARTICIPANT.

Study Staff enter:

Study Site ID: _____

Participant ID

--	--	--	--

Date

____	/	____	/	_____
MM		DD		YYYY

Thank you for agreeing to complete this questionnaire. Your responses will be kept confidential. To keep the information you provide private, personal information (name, address, phone number) will NOT be collected in this questionnaire. Before you begin, there are a few practice questions for you to get used to how the system works. If you have any questions on how to use the computer, the clinic staff can assist you.

If you prefer not to respond to a question, you may leave a question blank and click the "NEXT" button to go to the next question.

Click the "NEXT" button to go to the next screen.

Introduction [Page 2]

Good! You can always move to the next screen by clicking "next", or, to go to the previous screen, click "back."

Click the "NEXT" button to go to the next screen.

Practice [Question 1]

This question shows how to answer questions with click boxes. Try answering the question below by moving the mouse arrow and clicking on boxes that match your choices.

PRACTICE QUESTION:

Which items do you like to eat on a salad? *Choose all that apply.*

[Answer options]

- Eggs
- Cheese
- Croutons
- Salad Dressing
- Carrots
- Bacon bits

This is an example of a question where more than one answer is allowed:

If you want to change your response, click the response you don't want again to de-select it and then select the answer(s) you do want.

Practice [Question 2]

Do you like summer?

- Yes
- No

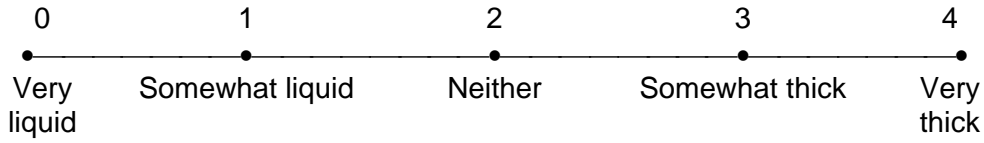
This is an example of a single response question:

If you want to change your response, simply click the response you want.

Practice [Question 3]

This screen is the last question type in this interview, and involves clicking on the point in the scale that most closely matches how you feel. Use the mouse to move the arrow to the desired place on the scale, and then click to make your choice.

PRACTICE QUESTION:
How thick do you like soup to be?



Ok. If you had any problem answering the prior questions, let the study staff know about it.
Otherwise, click "NEXT" and proceed with the first questionnaire.

SECTION A. DEMOGRAPHICS

1. How old are you? _____ (In years) [18-65]

[IF Q 1 > 24, PRESENT PROMPT "I want to confirm your age. You entered XX. Is that correct?" IF NO, THEN PROMPT TO REENTER AGE IN Q 1]

2. Please indicate the highest education level you achieved

1. eighth grade or lower
2. partial high school
3. high school graduate
4. partial college
5. college graduate
6. partial graduate school
7. graduate school degree

3. Do you consider yourself...

- _____ 1. Hispanic or Latina? [SKIP TO Q 5]
_____ 2. Not Hispanic or Latina?

4. Do you consider yourself...

1. African-American or Black
2. Asian or Pacific Islander
3. White or European American
4. Native American
5. Other

5. Do you consider yourself ...

- _____ 1. Lesbian/gay/homosexual?
_____ 2. Bisexual?
_____ 3. Straight/heterosexual?
_____ 4. Undecided
_____ 5. Other

6. Are you ...

1. working full time
2. working part-time
3. on disability
4. not working

7. Are you ...

1. in school full time
2. in school part-time
3. on vacation now but in school
4. not in school at all now

8. Please check what describes who you live with now...

1. You live alone in an apartment or house
2. You live alone in a dormitory
3. You live with a partner or spouse
4. You live with parent(s) or other family members
5. You live with friends and/or roommates
6. You are homeless or do not have a regular place to live now

9 What is your total **personal** income before taxes from all sources per month or per year?

Please select if you would like to answer this question for the past month or the past year...

Month: _____

Year: _____

SECTION B. SEXUAL BEHAVIOR

Let's briefly go over the definitions of some terms so that you understand what is being asked.

When I say:	I mean:
Vaginal Sex:	When a man or boy inserts his penis into your vagina.
Receptive Anal Sex:	When a man or boy puts his penis into your anus (or butt).
Receiving Oral Sex:	When a partner puts his or her mouth or tongue on your vagina, or anus (or butt).
Giving oral sex	When you put your mouth or tongue on your partner's penis, vagina or anus (or butt).

10. How old were you the first time you had vaginal sex? If you have never had vaginal sex, put "0" as your response.

11. How old were you the first time you had anal sex? If you have never had anal sex, put "0" as your response. [IF Q 11 = 0, SKIP Q 22 - 24b_3]

12. How old were you the first time you gave someone oral sex? If you have never given oral sex, put "0" as your response. [IF Q 12 = 0, SKIP Q 27]

13. How old were you the first time you received oral sex? If you have never gotten oral sex, put "0" as your response. [IF Q 13 = 0, SKIP Q 28]

AGE MUST BE <= AGE AT TIME OF INTERVIEW (Q#1). IF AGE ENTERED IS > AGE AT TIME OF INTERVIEW (Q#1) SHOW PROMPT, "You have entered an invalid age. Please re-enter." IN ADDITION, PROGRAM A SOFT RANGE CHECK SO ANY RESPONSE >0 AND <10 RECEIVES PROMPT THAT READS, "I want to confirm the age that you first had vaginal or anal or oral sex. You entered _____. Is that correct?"

Now I am going to ask you about your sexual partners. By sexual partner I mean someone who you've had vaginal or anal sex with.

14. Think about all the male partners you have had sex with in your lifetime. In your whole lifetime, how many different male partners have you had sex with, either vaginal or anal?

15. Think about all the female partners you have had sex with in your lifetime. In your whole lifetime, how many different female partners have you had sex with, either vaginal or anal?

ACCEPTABLE RANGE FOR (Q#14) IS 1 – 10,000 BUT INCLUDE SOFT RANGE CHECK FOR ANY RESPONSE >100. PROMPT SHOULD READ, "I want to confirm the number of different partners that you have had sex with in your lifetime. You have entered _____. Is that correct?" IF RESPONSE IS 0 SHOW PROMPT THAT READS, "You have entered an invalid number. Please re-enter."

Now I'd like you to take a moment to think back about your sex life during the past 90 days. [INSERT TIMELINE REMINDER HERE] — that is, since [DATE]. I'm going to ask you some questions about the sex you have had during that period.

PROGRAM TO CALCULATE DATE OF 90 DAYS PRIOR TO INTERVIEW DATE AND INSERT AS NEEDED.

16. How many male partners have you had vaginal sex with in the past 90 days, that is since [DATE]?

ACCEPTABLE RANGE FOR Q#16 IS 0 – 10,000, BUT INCLUDE SOFT RANGE CHECK FOR ANY RESPONSE >100. IF RANGE FAILURE, SHOW PROMPT THAT READS, "I want to confirm the number of different partners that you have had sex with in the past 90 days. You have entered _____. Is that correct?"

17a. How many times did a male partner put his penis in your vagina in the past 90 days, that is since [DATE]?

17b. How many times did a male partner put his penis in your vagina without a condom in the past 90 days, that is since [DATE]?

18. How many different male partners put their penises in your vagina without a condom in the past 90 days, that is since [DATE]?

. IF Q 18 > 1 (i.e., THE PARTICIPANT REPORTS THAT MORE THAN ONE MAN PENETRATED HER VAGINA WITHOUT A CONDOM), SKIP TO Q 20. IF Q 18 = 1, ASK Q 19 AND SKIP Q 20

You said that one partner put his penis in your vagina without a condom.

19. Regarding this partner (please select one answer).....

- ___ a. This partner told you he was HIV negative and you had no reason to doubt it.
- ___ b. You knew this partner was HIV positive.

___ c. You were not completely sure of this partner's HIV status.

You said ___ men [INSERT THE NUMBER FROM Q 18] put their penises in your vagina without a condom. (If this number is incorrect, please click on the "BACK" button and change your previous answer.)

Of those men...

20_1. how many had actually told you they were HIV-negative and you had no reasons to doubt it?

20_2. how many do you know to be HIV-positive?

20_3. how many were you NOT completely sure of their HIV status?

[NOTE: NUMBERS FOR THE PREVIOUS THREE QUESTIONS ARE BASED ON THE WAY VARIABLES WILL BE LISTED IN THE DATA OUTPUT FILE. THEREFORE QUESTION # 21 DOES NOT EXIST.]

IF Q 11 = 0, SKIP Q 22 - 24

22. Now I'd like to ask you about receptive anal sex. Remember, by receptive anal sex, I mean when a man or boy puts his penis inside your anus or butt. During the past 90 days, did you have receptive anal sex with any male partners?

- 0. No
- 1. Yes

22a. How many male partners put their penises in your anus or butt during the past 90 days?

23a. How many times did a male partner put his penis inside your anus or butt during the past 90 days, that is since [DATE]?

23b. How many times did a male partner put his penis inside your anus or butt without a condom during the past 90 days?

24. How many different male partners put their penises in your anus or butt without a condom during the past 90 days?

IF Q 24 > 1 (i.e., THE PARTICIPANT REPORTS THAT MORE THAN ONE MAN PENETRATED HER VAGINA WITHOUT A CONDOM), SKIP TO Q 24b. IF Q 24 = 1, ASK Q 24a AND SKIP Q 25

You said that one partner put his penis in your anus or butt without a condom.

24a. Regarding this partner (please select one answer)...

- a. This partner told you he was HIV negative and you had no reason to doubt it.
- b. You knew this partner was HIV positive.
- c. You were not completely sure of this partner's HIV status.

You said ___ men [INSERT THE NUMBER FROM 24] put their penises in your anus or butt without a condom. (If this number is incorrect, please click on the "BACK" button and change your previous answer.)

Of those men...

24b_1. how many had actually told you they were HIV-negative and you had no reasons to doubt it?

24b_2. how many do you know to be HIV-positive?

24b_3. how many were you NOT completely sure of their HIV status?

25. Still thinking about the past 90 days, I want to ask you some questions about all of the male partners that you had sex with, either vaginal or anal, during that period. First, during the past 90 days did you ever ask a partner to use a condom?

- 0. No
- 1. Yes

IF Q 25 = 0, SKIP TO Q 27

26. Did any of your partners refuse to use a condom when you asked them?

- 0. No
- 1. Yes

IF Q 12 = 0, SKIP Q 27

27. Now I'd like to ask you about giving oral sex. By giving oral sex I mean when you put your mouth or tongue on your partner's penis, vagina or anus (or butt). During the past 90 days, did you have oral sex with any of your partners, either male or female?

- 0. No
- 1. Yes

IF Q 13 = 0, SKIP Q 28 AND GO TO INSTRUCTIONS ABOVE Q 29

28. Now I'd like to ask you about receiving oral sex. By receiving oral sex I mean when your partner puts his or her mouth or tongue on your vagina, or anus (or butt). During the past 90 days, did you receive oral sex from any of your partners?

- 0. No
- 1. Yes

PARTNER DATA

The next set of questions is about your most recent sex partner(s). You are going to be asked some questions about these partners. Let's briefly go over the definitions of some terms so that you understand what is being asked.

A main male partner is someone that you have sex with and you consider this person to be a person that you are serious about. A main partner is someone with whom you have an ongoing relationship and who you have sex with often - like a spouse, lover, or boyfriend.

A casual male partner is someone that you have sex with two or more times but do not consider this person to be a main partner to you. A casual partner is someone with whom you have sex occasionally on a casual basis.

A one-time male partner is someone with whom you had sex one time and don't plan to have sex with again.

29. How many main male partners have you had in the past 90 days? If you did not have a main partner, put "0" as your response.

30. How many casual male partners have you had in the past 90 days? If you did not have a casual partner, put "0" as your response.

31. How many one-time male partners did you have in the past 90 days? If you did not have a one-time partner, put "0" as your response.

32. Thinking about the male person with whom you most recently had sexual intercourse, is this partner:

1. A main partner
2. A casual partner
3. A one-time partner

THE FOLLOWING QUESTIONS WILL BE ASKED FOR MOST RECENT MAIN PARTNER. IF Q 29 = 0, SKIP Q 33 THROUGH Q 39.

MAIN PARTNER

You indicated that you currently have or that you have had a main partner in the past 90 days. The following set of questions will ask about your most recent male main partner.

33. How old is or how old was this most recent main partner at the time you were together?

AGE

Don't Know/Unsure.....99

ACCEPTABLE AGE RANGE IS 01-99. IF RANGE FAILURE, SHOW PROMPT THAT READS, "I want to confirm the age of your most recent main partner. You have entered _____. Is this correct? IF AGE ENTERED IS 0 SHOW PROMPT THAT READS, "You have entered an invalid age. Please re-enter." ALSO ADD A SOFT RANGE CHECK TO CONFIRM ANY AGES <10 OR >40.

34. What is this most recent main partner's racial/ethnic background?

- 1. Asian/Pacific Islander
- 2. Black/African American
- 3. Native American/Alaskan Native
- 4. Hispanic/Latino
- 5. White
- 6. Other or mixed race

35. How many times did you have sex, either vaginal or anal sex, with this most recent main partner during the last 90 days?

FIELD SHOULD ALLOW A FOUR-DIGIT NUMBER, BUT PROGRAM A SOFT RANGE CHECK WITH RANGE FAILURE FOR ANY RESPONSE OVER 300. IF RANGE FAILURE, SHOW PROMPT THAT READS, "I want to confirm the number of times you had sex, either vaginal or anal sex, with this most recent main partner. You entered _____. Is that correct?"

36. Of those times [INSERT NUMBER FROM Q35 ABOVE] how many times did you use a condom with this most recent main partner?

37. The last time you had sex with this most recent main partner, what did you use to keep from getting pregnant? Choose all that apply.

- 1. Condoms
- 2. Pill
- 3. Depo-Provera shot
- 4. Norplant or Implanon
- 5. Withdrawal
- 6. Ortho Patch
- 7. Ring
- 8. Rhythm
- 9. IUD (e.g., Mirena® or Copper T)
- 10. Nothing
- 11. Other

38. Did you ask this most recent main partner whether he had been tested for HIV, or did this partner tell you that he had been tested for HIV?

- 0. No
- 1. Yes

IF Q 38 = 0, SKIP Q 39

39. What were your partner's test results?

- 1. HIV positive
 - 2. HIV negative
 - 3. Partner did not tell me test results
 - 4. Partner did not go back for test results
-

SECTION C. VAGINAL DOUCHES, LUBRICANTS, AND OTHER PRODUCTS (Name of products will be tailored to study site)

The next set of questions is about vaginal products.

40. Have you ever used a tampon?
0. No [GO TO Q 42]
1. Yes
41. Have you used tampons with applicators, without applicators, or both?
a. with applicators
b. without applicators
c. both
42. Have you ever used a cervical cap?
0. No
1. Yes

Please indicate if you have ever used any of the following products:

43. Dessicants, that is, anything to make your vagina dry or tight, such as Tight Stuff
0. No
1. Yes
44. Female condoms, also called "Reality®"
0. No
1. Yes
45. Vaginal moisturizers or sex lubricants, such as Lubrin, Replens, Moist Again, or KY jelly or liquid
0. No
1. Yes
46. Medications for yeast infections that you put in your vagina such as Monistat, Femstat, or Gyne-Lotrimin
0. No
1. Yes
47. Spermicides, that is, a foam, gel, film, suppository, or cream that kills sperm and prevents pregnancy
0. No
1. Yes

The following questions refer to use of vaginal douches.

48. Have you ever used a vaginal douche? By vaginal douche we mean something you use to squirt a liquid into your vagina.
0. No [GO TO NEXT SECTION (Q 52)]
1. Yes

49. How many times did you douche vaginally in the past 3 (three) months?

___ ___ ___ [IF '0,' GO TO NEXT SECTION (Q 52)] [0-999]

50. Of the times you douched in the past 3 months, how many times did you douche... [Indicate all that apply] [1-999]

- a. for general hygiene _____
- b. in preparation for sex _____
- c. after sex _____
- d. for pleasure _____
- e. after your period was finished _____
- f. while you were bleeding from your period _____
- g. because your vagina felt itchy or uncomfortable _____
- h. other _____

51. When you douched in the past 3 (three) months, how many times did you use... [Indicate all that apply] [1-999]

- a. A hand-held hose or bidet _____
 - b. Over-the-counter disposable douche product (e.g., Massengill® or Summer's Eve®) _____
 - c. Re-usable bottle system _____
 - d. Water and vinegar _____
 - e. Other _____
-

SECTION D. LUBRICANT USE FOR SEX

The following questions refer to commercial sexual lubricants. This does not include saliva or the lubricant that comes with condoms but is lubricant you bought over the counter or in a store.

52. Have you ever used a commercial lubricant during vaginal intercourse?

0. No [SKIP TO Q 66]

1. Yes

53. During the past 3 months, how frequently have you had vaginal intercourse using a commercial sexual lubricant?

_____ 0 Never [SKIP to Q 66]

_____ 1 Sometimes

_____ 2 Always

54. What types of lubricant have you used? [Indicate all that apply]

_____ 1 Silicon-based (e.g., Eros)

_____ 2 Water-based (e.g., KY, Wet)

_____ 3 Oil-based (e.g., Crisco)

55. Where do you usually get your lubricant from?

_____ 1 Sex shop

_____ 2 Pharmacy/drug store

_____ 3 AIDS Agency

_____ 4 Bar, disco, sex club

_____ 5 Online

_____ 6 Other

56. Do you prefer a lubricant with ...

_____ 0 No flavor

_____ 1 Flavor

_____ 2 It doesn't matter

57. Do you prefer a lubricant with ...

_____ 0 No color/transparent

_____ 1 Color

_____ 2 It doesn't matter

58. Do you prefer a lubricant with ...

_____ 0 No smell

_____ 1 Smell

_____ 2 It doesn't matter

59. In terms of commercial lubricant consistency, what do you prefer?

0 1 2 3 4

Very liquid Somewhat liquid Neither Somewhat thick Very thick

60. Describe the ideal type of dispenser for a lubricant.
- 1 Tube (like toothpaste or KY®)
 - 2 Pump (like in Vaseline Intensive Care® or Wet®)
 - 3 Containers with pop-up covers
 - 4 Can or jar
 - 5 Single use
 - 6 Disposable tube
 - 7 Other
61. In general when you have vaginal intercourse, is the lubricant applied...[Indicate all that apply]
- 1 Directly on your partner's penis?
 - 2 On the outside of your vagina?
 - 3 Inside your vagina?
 - 4 Inside the condom?
 - 5 On the outside of the condom?
 - 6 Other
62. When you are having vaginal intercourse, who applies the lubricant?
- 0 Self
 - 1 Partner
 - 2 Both
63. When is the lubricant first applied?
- 0 Before there is any sexual contact
 - 1 During sex but before he penetrates you
 - 2 After he first penetrates you if you feel the need for it
64. How frequently do you usually reapply the commercial lubricant during intercourse?
- 0 Never
 - 1 Once
 - 2 Twice
 - 3 3 times or more
65. From your past experience, does the application of the lubricant interrupt sex?
- 0 It does not interrupt sex
 - 1 It interrupts sex but does not bother me
 - 2 It interrupts sex and bothers me

IF Q11 = 0 (NEVER HAD ANAL INTERCOURSE), SKIP TO NEXT SECTION (Q 72).

66. Have you ever used a commercial lubricant during anal intercourse?
- 0. No [SKIP TO NEXT SECTION (Q 72)]
 - 1. Yes

67. What types of lubricant have you used? [Indicate all that apply]
- 1 Silicon-based (e.g., Eros[®])
 - 2 Water-based (e.g., KY[®], Wet[®])
 - 3 Oil-based (e.g., Crisco[®])
68. Describe the ideal type of dispenser for a lubricant.
- 1 Tube (like toothpaste or KY[®])
 - 2 Pump (like in Vaseline Intensive Care[®] or Wet[®])
 - 3 Containers with pop-up covers
 - 4 Can or jar
 - 5 Single use
 - 6 Disposable tube
 - 7 Other
69. In general when you have anal intercourse, is the lubricant applied...[Indicate all that apply]
- 1 Directly on your partner's penis?
 - 2 Around your anus (rim)?
 - 3 Inside your anus?
 - 4 Inside the condom?
 - 5 On the outside of the condom?
 - 6 Other
70. When you are having anal intercourse, who applies the lubricant?
- 0 Self
 - 1 Partner
 - 2 Both
71. When is the lubricant first applied?
- 0 Before there is any sexual contact
 - 1 During sex but before he penetrates you
 - 2 After he first penetrates you if you feel the need for it
-

SECTION E. SUBSTANCE USE & HIV TESTING HISTORY

The following questions refer to alcohol and drug use. Now I will show you a list of different drugs.

GO DOWN "A" COLUMN FIRST. IF "0" FOR ANY SUBSTANCES, SKIP B FOR THOSE PARTICULAR SUBSTANCES. USE THE FOLLOWING RESPONSE CHOICES:

- 0 = Never/none
- 1 = Once a month or less
- 2 = 2-3 times a month
- 3 = About once a week
- 4 = 2-6 times a week
- 5 = About once a day
- 6 = More than once a day

A. During the last 90 days, how often have you used [INSERT SUBSTANCE]

B. Of those times during the past 90 days, how often have you used [INSERT SUBSTANCE] immediately before or during sexual intercourse?

	[A] Number of times used PAST 3 MONTHS	[B] Number of times used before or during SEX PAST 3 MONTHS
72. Alcohol (beer, wine, liquor)?		
73. Marijuana/hashish/Pot/Weed?		
74. Ecstasy/MDMA?		
75. Crystal Meth/Amphetamines/ Methamphetamines/Speed/Crank/ Ice?		
76. Ketamine/Special K?		
77. GHB (Gamma Hydroxybutyrate)?		
78. Other Hallucinogens/LSD/ Mushrooms?		
79. Poppers/Amyl Nitrite/Butyl Nitrite?		
80. Crack?		
81. Cocaine (not Crack)?		
82. Heroin?		
83. DELETED		

84. Other pharmaceutical drugs not prescribed to you by a physician (Percocet or similar drugs?		
---	--	--

85. Thinking about the times you used alcohol during the last 90 days, how much did you typically use?

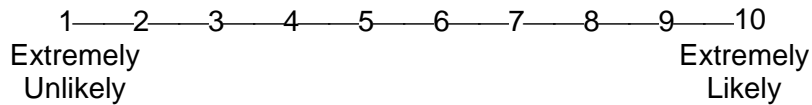
- 0. Too little to feel any effect
- 1. Enough to feel it a little
- 2. Enough to feel it a lot
- 3. Enough to get drunk
- 4. Enough to feel like you might pass out

86. How many times in total have you been tested for HIV? If never, enter 0.

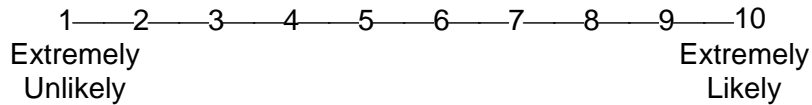
SECTION F. LIKELIHOOD OF USING MICROBICIDE IN THE FUTURE

Scientists are trying to develop alternatives to condoms for the prevention of HIV transmission during intercourse. In this study, we are interested in gels, and enemas or douches.

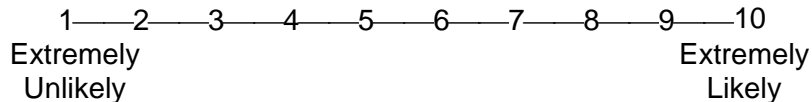
87. If a vaginal microbicide were available that provided some protection against HIV, and it was a gel, how likely would you be to use it every time you have vaginal intercourse?



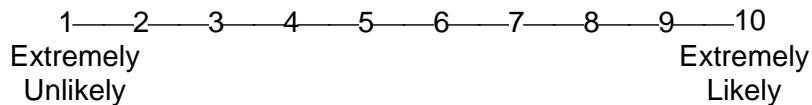
88. If a rectal microbicide were available that provided some protection against HIV, and it was a gel, how likely would you be to use it every time you have anal intercourse?



89. If using a vaginal douche before having intercourse provided some extra protection against HIV, how likely would you be to give yourself a vaginal douche prior to every time you have vaginal intercourse?



90. If using an enema before having anal intercourse provided some extra protection against HIV, how likely would you be to give yourself an enema prior to every time you have anal intercourse?



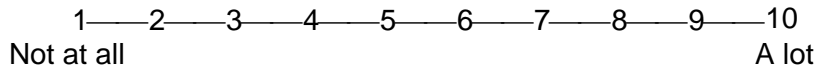
SECTION G. PLEASURE

Please read the following list of sexual behaviors and indicate **how much you would like doing each behavior WITH MEN if it were not for AIDS.** Please answer each question regardless of whether you have ever done it or plan to do it in the future.

	Dislike very much	Dislike somewhat	Dislike slightly	Like slightly	Like somewhat	Like very much
91. Having vaginal intercourse WITHOUT a condom	1	2	3	4	5	6
92. Having vaginal intercourse WITH a condom	1	2	3	4	5	6
93. Having your partner ejaculate inside your vagina WITHOUT a condom	1	2	3	4	5	6

Please indicate:

94. How much do condoms interfere with your sexual satisfaction when you are penetrated vaginally?



IF Q11 = 0 (NEVER HAD ANAL INTERCOURSE), SKIP Q 95 - 98 and END QUESTIONNAIRE HERE. "You have completed the interview. Thank you."

Please indicate **how much you would like doing each behavior WITH MEN if it were not for AIDS.** Please answer each question regardless of whether you have ever done it or plan to do it in the future. [ALLOW ONLY ONE ANSWER PER QUESTION.]

	Dislike very much	Dislike somewhat	Dislike slightly	Like slightly	Like somewhat	Like very much
95. Having anal intercourse WITHOUT a condom	1	2	3	4	5	6
96. Having anal intercourse WITH a condom	1	2	3	4	5	6
97. Having your partner ejaculate inside your rectum WITHOUT a condom	1	2	3	4	5	6

98. How much do condoms interfere with your sexual satisfaction when you are penetrated anally?

1—2—3—4—5—6—7—8—9—10
Not at all A lot

You have completed the interview. Thank you

Section II: Acceptability and Adherence Questionnaire

Table of Contents

Section:	Title:	Pages:
A	PRODUCT ACCEPTABILITY (VAGINAL USE)	26-27
B	PRODUCT ADHERENCE	28
C	APPLICATION PROCESS	29
D	APPLICATOR	30
E	CHANGES IN VOLUME USED	31
F	EXPERIENCES USING THE PRODUCT	32
G	SEXUAL INTERCOURSE USING THE PRODUCT	33-34
H	PARTNER'S REACTION	35-36
I	SEXUAL ENJOYMENT AFTER PRODUCT USE	37
J	CONDOMS	38
K	CHANGES IN SEXUAL PRACTICES DUE TO PRODUCT USE	39
L	LIKELIHOOD OF USING PRODUCT IN THE FUTURE	40
M	WILLINGNESS TO USE HIGHER VOLUME	41
N	POSSIBILITY OF COVERT USE	42

Study Staff enter:

Study Site ID: _____

Participant ID

--	--	--	--

Date

/	/	_____
MM	DD	YYYY

SECTION A. PRODUCT ACCEPTABILITY

1. Overall (i.e., considering all the episodes in which you used this gel) how much did you like the gel?

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

2. How much did you like the color of the gel?

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

3. How much did you like the taste of the gel?

[99] Don't know, I did not taste the gel

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

4. How much did you like the smell of the gel?

[99] Don't know, I did not smell the gel

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

5. How much did you like the consistency of the gel (how thick or thin it was)?

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

6. How much did you like how the gel felt inside your vagina immediately after inserting it?

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

7. How much did you like how the gel felt inside your vagina 30 minutes after inserting it?

[99] Don't know, I did not have the gel in my vagina for 30 minutes

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

8. Did the gel feel...

1—2—3—4—5—6—7—8—9—10
Too runny About right Too sticky

SECTION B. PRODUCT ADHERENCE

9. You were asked to insert the gel in your vagina twice a day for 14 days. However, different circumstances may have prevented you from doing it every time. Please indicate the total number of times you used the gel during the trial period.

_____ [range 0 – 30]

[SKIP Q10 IF Q9 IS = OR > THAN 28]

10. Please check all that apply if any of the following reasons prevented you from using the gel.

- I forgot
 - I did not have the gel with me
 - My sexual partner did not want me to use the gel
 - I did not like how the gel felt inside me
 - I had vaginal bleeding and decided to stop using the gel
 - I got my period
 - I had a burning sensation when using the gel
 - I had an itching sensation when using the gel
 - The gel kept leaking out
 - The gel was messy
 - I did not want to use the gel
 - Other
-

SECTION C. APPLICATION PROCESS

11. Overall, how much did you like putting the gel inside your vagina?

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

12. How easy was it to put the gel inside your vagina?

1—2—3—4—5—6—7—8—9—10
Very Neither easy Very
difficult nor difficult Easy

13. Where were you at the time you put the gel inside your vagina? (Check all that apply.)

1. Bathroom
2. Bedroom
3. Other

14. What position did you typically use to put the gel inside your vagina? [CASI ALLOW ONLY ONE ANSWER.]

1. Kneeling
 2. Laying on side
 3. Standing
 4. Squatting or seated over toilet or tub
 5. Other
-

SECTION D. APPLICATOR

15. How much did you like the gel applicator (the device you used to deliver the gel inside your vagina)?

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

16. Did you have any problems with the applicator used to deliver the gel in your vagina?

- 0. No
- 1. Yes

17. How easy would it be to carry this gel around if you needed to?

1—2—3—4—5—6—7—8—9—10
Extremely Neither easy Extremely
difficult nor difficult easy

18. How easy would it be for you to store this gel?

1—2—3—4—5—6—7—8—9—10
Extremely Neither easy Extremely
difficult nor difficult easy

19. How concerned would you be if someone found out that you have this gel in storage?

1—2—3—4—5—6—7—8—9—10
Extremely Not concerned
concerned at all

SECTION E. CHANGES IN VOLUME USED

20. Did you ever use less than the full amount of gel that came in each applicator?
[0] No [SKIP TO NEXT SECTION]
[1] Yes
21. If so, on how many occasions did you use less than the full amount of gel?
[1] 1 of the occasions
[2] 2 of the occasions
[3] On 3 or more of the occasions
22. When you used less than the full amount, about how much did you use, on average?
[1] Three quarters of the dose
[2] Half of the dose
[3] One quarter of the dose
23. Please indicate the reason why you used less than the full amount of gel? (check all that apply)
[1] It was too messy
[2] It leaked
[3] I was scared it could be bad for me
[4] I had trouble using the applicator
[5] Other
-

SECTION F. EXPERIENCES USING THE PRODUCT

24. Did you have any problems using this gel?

- [0] No
- [1] Yes

25. Did you experience any leakage after you used the gel?

- [0] None [SKIP TO Q 27]
- [1] Some
- [2] A lot

26. How much were you bothered by leakage?

1—2—3—4—5—6—7—8—9—10
Not at all Very much

27. Did you experience any gel leakage onto your underwear or bed sheets?

- [0] None [SKIP TO NEXT SECTION (Q 29)]
- [1] Some
- [2] A lot

28. How much were you bothered by gel leakage onto your underwear or bed sheets?

1—2—3—4—5—6—7—8—9—10
Not at all Very much

SECTION G. SEXUAL INTERCOURSE USING THE PRODUCT

During this study...

29. How many male partners did you have vaginal intercourse with? ____
By vaginal intercourse, we mean when a man or boy inserts his penis into your vagina.

IF Q 29 = 0, SKIP Q 30 - 34 AND GO TO Q 35.

30. How many times did you have vaginal intercourse? ____

31. How many times did you have vaginal intercourse using the gel with condoms? ____

32a. How many times did you have vaginal intercourse using the gel without condoms?

32b. How many times did you have vaginal intercourse using condoms without the gel?

33. How many times did you have vaginal intercourse using neither gel nor condoms?

34. With how many partners did you use the gel during vaginal intercourse? ____

NUMBER OF PARTNERS MUST BE \leq RESPONSE GIVEN IN Q 29. IF Q 34 $>$ Q 29, SHOW PROMPT, "You indicated that you had vaginal intercourse with XX number of partners during this study. Yet, you just indicated that you used the gel during vaginal intercourse with XX number of partners. If this is incorrect, please re-enter your response. Otherwise, go back to question # 29 to correct your response to that question."

During this study...

35. How many male partners did you have anal intercourse with? ____

By anal intercourse, we mean when a man or boy inserts his penis into your anus (or butt).

IF Q 35 = 0, SKIP Q 36 - 40 AND GO TO NEXT SECTION (Q 41).

36. How many times did you have anal intercourse? ____

37. How many times did you have anal intercourse using the gel in your anus or rectum (or butt) with condoms? ____

38a. How many times did you have anal intercourse using the gel in your anus or rectum (or butt) without condoms? ____

38b. How many times did you have anal intercourse using condoms without the gel in your anus or rectum (or butt)?

39. How many times did you have anal intercourse using neither gel nor condoms?

40. With how many partners did you use the gel during anal intercourse? ____

NUMBER OF PARTNERS MUST BE \leq RESPONSE GIVEN IN Q 35. IF Q 40 > Q 35, SHOW PROMPT, "You indicated that you had anal intercourse with XX number of partners during this study. Yet, you just indicated that you used the gel during anal intercourse with XX number of partners. If this is incorrect, please re-enter your response. Otherwise, go back to question # 35 to correct your response to that question."

SECTION H. PARTNER'S REACTION

Let us remind you what we mean by a main, casual, and one-time male partner.

A main male partner is someone that you have sex with and you consider this person to be a person that you are serious about. A main partner is someone with whom you have an ongoing relationship and who you have sex with often - like a spouse, lover, or boyfriend.

A casual male partner is someone that you have sex with two or more times but do not consider this person to be a main partner to you. A casual partner is someone with whom you have sex occasionally on a casual basis.

A one-time male partner is someone with whom you had sex one time and don't plan to have sex with again.

41. With what type of partner did you use the gel during vaginal or anal intercourse?

Select all that apply.

- 1. Main partner
- 2. Casual partner
- 3. One-time partner

42. Were any of your partners aware that you used this gel?

[0] No [SKIP Q 43, GO TO INSTRUCTIONS ABOVE Q 44]

[1] Yes

43. Which type of partners was aware that you had used this gel? Select all that apply.

- 1. Main partner(s)
- 2. Casual partner(s)
- 3. One-time partner(s)

IF IN Q 41 CHOICE 1 (MAIN PARTNER) IS NOT SELECTED, SKIP Q 44 AND GO TO INSTRUCTIONS ABOVE Q 45.

44. Overall, how much did your most recent main partner like the gel?

[99] Don't know

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

IF IN Q 41 CHOICE 2 (CASUAL PARTNER) IS NOT SELECTED, SKIP Q 45 AND GO TO INSTRUCTIONS ABOVE Q 46.

45. Overall, how much did your most recent casual partner like the gel?
[99] Don't know

1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

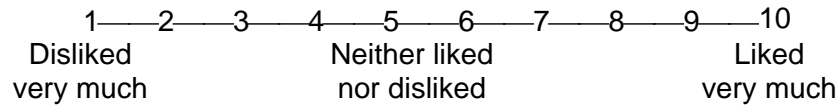
IF IN Q 41 CHOICE 3 (ONE-TIME PARTNER) IS NOT SELECTED, SKIP Q 46 AND GO TO NEXT SECTION (Q 47).

46. Overall, how much did your most recent one-time partner like the gel?
[99] Don't know

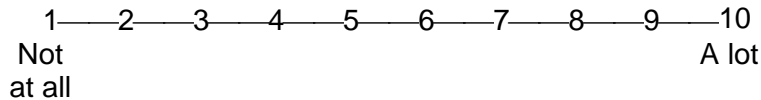
1—2—3—4—5—6—7—8—9—10
Disliked Neither liked Liked
very much nor disliked very much

SECTION I. SEXUAL ENJOYMENT AFTER PRODUCT USE

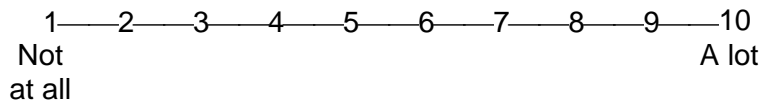
47. How much did you like vaginal intercourse when using the gel?



48. Overall, how sexually satisfied were you with vaginal sex when using the gel?

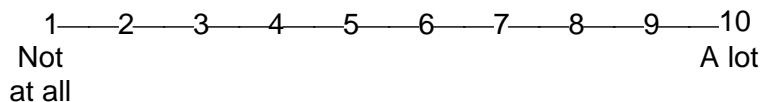


49. Overall, how sexually satisfied do you think your partner was after you used the gel? (If you used the gel with more than one partner, refer only to your most recent sexual partner.)



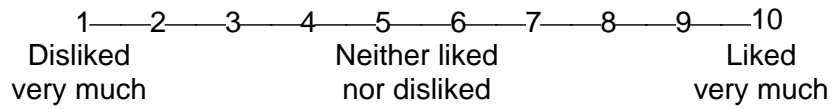
50. How sexually satisfied do you feel with this partner in general when you have vaginal intercourse NOT using this study gel?

[88] Not applicable, I only had sex with this partner using this study gel

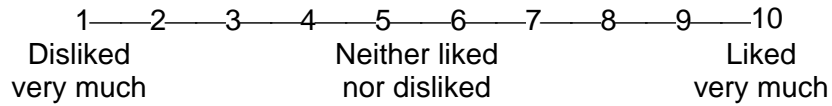


SECTION J. CONDOMS

51. How much did you like having intercourse with condoms after inserting the gel?



52. How much did you like having intercourse without condoms after inserting the gel?



SECTION K. CHANGES IN SEXUAL PRACTICES DUE TO PRODUCT USE

53. Thinking about your experience having vaginal sex after using this specific gel, was this better, worse, or no different from other occasions when you did not use this gel?

- [2] Better
- [1] Worse
- [0] No different [SKIP TO Q 55]

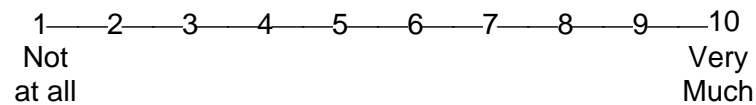
54. After you used the gel, was vaginal penetration easier?

- [0] No
- [1] Yes, penetration was somewhat easier
- [2] Yes, penetration was much easier

55. Did you ever have to interrupt sex to apply the gel?

- [0] No [SKIP TO NEXT SECTION]
- [1] Yes

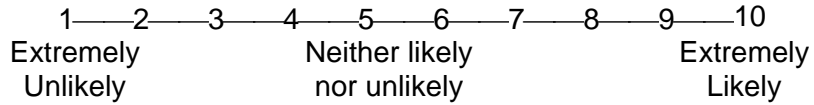
56. How much were you bothered by having to interrupt sex to apply the gel?



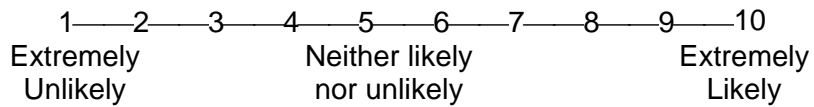
SECTION L. LIKELIHOOD OF USING PRODUCT IN THE FUTURE

GEL

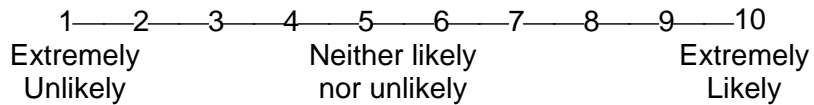
57. If a gel were available that provided some protection against HIV, and it looked like the one you have used in this study, how likely would you be to use it every time you have vaginal intercourse?



58. How likely would you be to use a gel that provided some protection against HIV on the occasions when you don't use condoms?



59. How likely would you be to use a gel if you had to wait 30 minutes after application before having intercourse?



60. How much would you be willing to spend on a gel per sexual occasion?

1. Half as much as one spends for condoms
2. About as much as one spends for condoms
3. Twice as much as one spends for condoms
4. Three times as much as one spends for condoms
5. Nothing, I would only use the gel if I could get it for free
6. Other

SECTION M. WILLINGNESS TO USE HIGHER VOLUME

Now, we do not yet know the volume of this gel that would be necessary to contribute to protect you against HIV during sex.

61a. Thinking about the amount of the gel you used, how likely would you be to use it every time you have vaginal intercourse if the same amount were required?

1—2—3—4—5—6—7—8—9—10
Extremely Unlikely Neither likely nor unlikely Extremely Likely

61b. Thinking about the amount of the gel you used, how likely would you be to use it every time you have vaginal intercourse if only half as much were required?

1—2—3—4—5—6—7—8—9—10
Extremely Unlikely Neither likely nor unlikely Extremely Likely

62. How likely would you be to use the gel every time you have vaginal intercourse if twice as much were required?

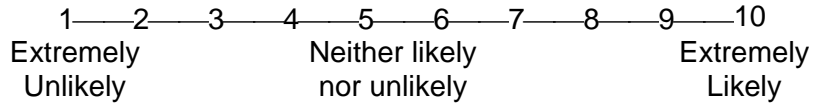
1—2—3—4—5—6—7—8—9—10
Extremely Unlikely Neither likely nor unlikely Extremely Likely

SECTION N. POSSIBILITY OF COVERT USE

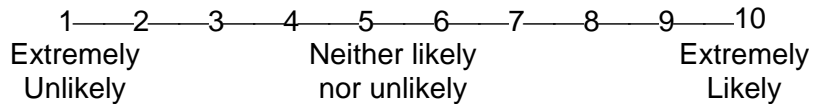
63. Would you want to use this gel without the knowledge of a main partner?

- [0] No
- [1] Yes

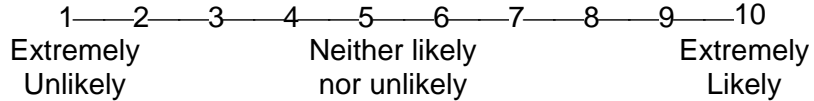
64. In your opinion, how likely would it be that your main male partner will notice the gel during sexual intercourse?



65. In your opinion, how likely would it be that your casual male partner will notice the gel during sexual intercourse?



66. In your opinion, how likely would it be that your one-time male partner will notice the gel during sexual intercourse?



You have completed the interview. Thank you

Section III: Study Burden Questionnaire

Table of Contents

Section:	Title:	Pages:
A.	STUDY BURDEN	45-46

Study Staff enter:

Study Site ID: _____

Participant ID

--	--	--	--

Date

____	/	____	/	_____
MM		DD		YYYY

SECTION A. STUDY BURDEN

The following questions refer to your feelings about participating in this study. Please tell us your level of agreement with the following statements

I was bothered by ...

1. The number of study visits
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree
2. The length of study visits
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree
3. Having to travel to study site
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree
4. The waiting time at study visits
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree
5. Having the pelvic exams
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree
6. Having the colposcopy (when the clinician looked inside my vagina with the magnifying instrument)
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree

7. Not being able to use vaginal douches during the study
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree

8. Not being able to use vaginal lubricants during the study
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree

9. Having to apply study gel each day
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree

10. Having to use study gel when I had sex
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree

11. Having to use condoms when I had sex during the study
 1. Strongly disagree
 2. Somewhat disagree
 3. Somewhat agree
 4. Strongly agree

12. Did you ever have a problem understanding the written instructions on how to use the gel?
[0] No
[1] Yes

13. Did you feel that your compensation for participation in this study was...
 1. Not enough
 2. About right
 3. More than enough

You have completed the interview. Thank you

Section Appendix 13-3

BEHAVIORAL MEASURES - SPANISH

Gracias por aceptar completar este cuestionario. Sus respuestas se mantendrán confidenciales. Para mantener privada la información que usted provee, no será recolectada información personal (nombre, dirección, número de teléfono) en este cuestionario. Antes de comenzar, hay algunas preguntas de práctica para que usted se familiarice con la forma en que el sistema funciona. Si tiene usted alguna pregunta sobre la forma de utilizar la computadora, el personal de la clínica puede ayudarle.

Si usted prefiere no responder a una pregunta, usted puede dejar en blanco una pregunta y hacer clic en el botón "SIGUIENTE" para ir a la próxima pregunta.

Haga clic en el botón "SIGUIENTE" para ir a la próxima pantalla.

Introducción [Página 2]

¡Muy bien! Usted puede pasar en cualquier momento a la siguiente pantalla oprimiendo "siguiente", o, regresar a la pantalla anterior haciendo clic en el botón "atrás (back)".

Haga clic en el botón "SIGUIENTE" para ir a la próxima pantalla.

Práctica [Pregunta 1]

Esta pregunta muestra la forma de responder preguntas utilizando recuadros. Intente contestar las siguientes preguntas moviendo la flecha (cursor) del ratón (mouse) y haciendo clic en los recuadros que concuerden con sus elecciones.

PREGUNTA DE PRÁCTICA:

¿Qué ingredientes le gusta comer en una ensalada? *Marque todas las que correspondan.*

[Opciones de Respuesta]

Huevos

Queso

Cubitos de pan (croutons)

Aderezo para ensalada

Zanahorias

Trozos de tocino

Este es un ejemplo de una pregunta en la cual se permite más de una respuesta: Si usted quiere modificar su respuesta, haga clic nuevamente en la respuesta que usted no desea para deseleccionarla y luego seleccione la(s) respuesta(s) que usted sí desea.

Práctica [Pregunta 2]

¿Le gusta el verano?

Sí

No

Este es un ejemplo de una pregunta de una sola respuesta:

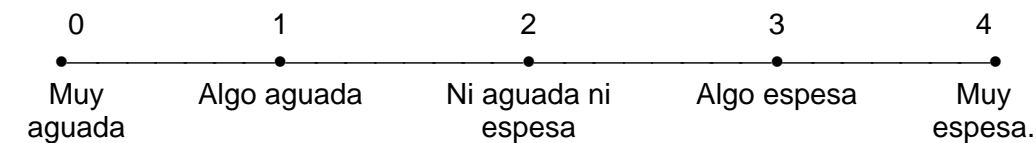
Si usted quiere modificar su respuesta simplemente haga clic en la respuesta deseada.

Práctica [Pregunta 3]

Esta pantalla es el último tipo de pregunta en esta entrevista, e implica hacer clic en el punto de la escala que mejor coincide con su forma de sentir. Utilice el ratón (mouse) para mover la flecha (cursor) hasta el lugar deseado en la escala, y luego haga clic para hacer su elección.

PREGUNTA DE PRÁCTICA:

¿Qué tan espesa le gusta que sea la sopa?



Ok. Si tuvo problemas para contestar estas preguntas, infórmelo al personal de estudio. En caso contrario, haga clic en "SIGUIENTE" y continúe con el primer cuestionario.

SECCIÓN A. DATOS DEMOGRÁFICOS

1. ¿Qué edad tiene usted? _____ (En años)
[18-65]
[IF Q 1 > 24, PRESENT PROMPT "Quiero confirmar su edad. Usted escribió _____. ¿Es esto correcto?" IF NO, THEN PROMPT TO REENTER AGE IN Q 1]
2. Por favor indique el nivel educativo más avanzado que usted obtuvo:
 8. octavo grado o menor
 9. secundaria incompleta
 10. graduado de escuela superior
 11. universidad incompleta
 12. graduado universitario
 13. maestría o doctorado incompleto
 14. título de maestría o doctorado
3. Usted se considera...
 - _____ 1. ¿Hispana o Latina? [VAYA A LA P 5]
 - _____ 2. ¿No Hispana ni Latina?
4. Usted se considera...
 6. Afro americana o Negra
 7. Asiática o Isleña del Pacífico
 8. Blanca o Europea Americana
 9. Americana Nativa
 10. Otro
5. Usted se considera
 - _____ 1. ¿Lesbiana/gay/homosexual?
 - _____ 2. ¿Bisexual?
 - _____ 3. ¿Atraída por el sexo opuesto/heterosexual?
 - _____ 4. Indecisa
 - _____ 5. Otro
6. En la actualidad...
 5. Trabaja Ttempo completo
 6. Trabaja medio tiempo
 7. Está incapacitado
 8. No trabaja
7. En la actualidad...
 5. Es estudiante de tiempo completo
 6. Es estudiante de medio tiempo
 7. Está de vacaciones pero es estudiante
 8. No está estudiando para nada
8. Por favor marque la opción que describa con quién vive actualmente...
 7. Vive sola en un departamento o casa
 8. Vive sola en un dormitorio
 9. Vive con una pareja o esposo

- 10. Vive con su(s) padre(s) u otros miembros de la familia
- 11. Vive con amigos y/o compañeros de habitación
- 12. No tiene casa o no tiene un lugar habitual para vivir por ahora

9. Antes de la deducción de impuestos ¿cuál es su ingreso **personal** total proveniente de todas sus fuentes de ingreso por mes o por año?

Por favor seleccione si desea contestar esta pregunta en relación con el último mes o con el último año...

Mes: _____

Año: _____

SECCIÓN B. COMPORTAMIENTO SEXUAL

Revisemos brevemente las definiciones de algunos términos para que entienda lo que se le pregunta.

Cuando digo:	Me refiero a:
Sexo Vaginal:	Cuando un hombre o muchacho introduce su pene en su vagina.
Sexo Anal Receptivo:	Cuando un hombre o muchacho introduce su pene en su ano (o nalgas).
Sexo Oral Receptivo:	Cuando una pareja coloca su boca o lengua en su vagina o ano (o nalgas).
Dar sexo oral:	Cuando usted coloca su boca o lengua en el pene, vagina o ano (o nalgas) de su pareja.

10. ¿Qué edad tenía usted la primera vez que tuvo sexo vaginal? Si usted nunca ha tenido sexo vaginal, ponga "0" como respuesta.

11. ¿Qué edad tenía usted la primera vez que tuvo sexo anal? Si usted nunca ha tenido sexo anal, ponga "0" como respuesta. [SI P 11 = 0, OMITA LAS P 22 - 24b_3]

12. ¿Qué edad tenía usted la primera vez que le dio a alguien sexo oral? Si usted nunca ha dado sexo oral, ponga "0" como respuesta. [SI P 12 = 0, OMITA LA P 27]

13. ¿Qué edad tenía usted la primera vez que recibió sexo oral? Si usted nunca ha dado recibido sexo oral, ponga "0" como respuesta. [SI P 13 = 0, OMITA LA P 28]

AGE MUST BE <= AGE AT TIME OF INTERVIEW (Q#1). IF AGE ENTERED IS > AGE AT TIME OF INTERVIEW (Q#1) SHOW PROMPT, "Ha escrito una edad no válida. Por favor escriba de nuevo." IN ADDITION, PROGRAM A SOFT RANGE CHECK SO ANY RESPONSE >0 AND <10 RECEIVES PROMPT THAT READS, "Quiero confirmar la edad en la que usted tuvo por primera vez sexo vaginal o anal u oral. Usted escribió _____. ¿Es esto correcto?"

Ahora le preguntaré sobre sus parejas sexuales. Al decir pareja sexual me refiero a alguien con quien haya tenido sexo vaginal o anal.

14. Piense en todas las parejas masculinas con quienes ha tenido sexo en su vida. Durante toda su vida, ¿con cuántas distintas parejas masculinas ha tenido sexo, ya sea vaginal o anal?

15. Piense en todas las parejas femeninas con quienes ha tenido sexo en su vida. Durante toda su vida, ¿con cuántas distintas parejas femeninas ha tenido sexo, ya sea vaginal o anal?

ACCEPTABLE RANGE FOR (Q#14) IS 1 – 10,000 BUT INCLUDE SOFT RANGE CHECK FOR

ANY RESPONSE >100. PROMPT SHOULD READ, "Quiero confirmar el número de parejas distintas con las que ha tenido sexo durante toda su vida. Usted ha escrito _____. ¿Es esto correcto?" IF RESPONSE IS 0 SHOW PROMPT THAT READS, "Ha escrito un número no válido. Por favor escriba de nuevo."

Ahora le pido que se tome un momento para recordar su vida sexual durante los últimos 90 días. [INSERT TIMELINE REMINDER HERE] — esto es, desde [DATE]. Le voy a hacer algunas preguntas sobre el sexo que tuvo durante ese período.

PROGRAM TO CALCULATE DATE OF 90 DAYS PRIOR TO INTERVIEW DATE AND INSERT AS NEEDED.

16. ¿Con cuántas parejas masculinas ha tenido sexo vaginal en los últimos 90 días, esto es desde [DATE]?

ACCEPTABLE RANGE FOR Q#16 IS 0 – 10,000, BUT INCLUDE SOFT RANGE CHECK FOR ANY RESPONSE >100. IF RANGE FAILURE, SHOW PROMPT THAT READS, "Quiero confirmar el número de parejas distintas con las que ha tenido sexo durante los últimos 90 días. Usted ha escrito _____. ¿Es esto correcto?"

17a. ¿En cuántas ocasiones ha introducido una pareja masculina su pene en su vagina en los últimos 90 días, esto es desde [DATE]?

17b. ¿En cuántas ocasiones ha introducido una pareja masculina su pene en su vagina sin utilizar condón en los últimos 90 días, esto es desde [DATE]?

IF RESPONSE IS > # IN Q 16, SHOW PROMPT THAT READS, "Quiero confirmar el número de parejas distintas con las que ha tenido sexo en los últimos 90 días. Usted ha escrito _____. ¿Es esto correcto?"

18. ¿Cuántas parejas masculinas distintas han introducido sus penes en su vagina sin utilizar condón en los últimos 90 días, esto es desde [DATE]?

IF Q 18 = 0, SKIP TO Q 22. IF Q 18 > 1 (i.e., THE PARTICIPANT REPORTS THAT MORE THAN ONE MAN PENETRATED HER VAGINA WITHOUT A CONDOM), SKIP TO Q 20. IF Q 18 = 1, ASK Q 19 AND SKIP Q 20

Usted dijo que una pareja introdujo su pene en su vagina sin condón.

19. En relación con esta pareja (por favor seleccione una respuesta).....

- ___ a. Esta pareja le dijo que era VIH negativo y usted no tenía razón para dudarlo.
- ___ b. Usted sabía que esta pareja era VIH positivo.
- ___ c. Usted no estaba completamente segura del estado de VIH de esta pareja.

Usted dijo que ___ hombres [INSERT THE NUMBER FROM Q 18] introdujeron su pene en su vagina sin condón. (Si este número es incorrecto, por favor haga clic en el botón "ATRÁS" (BACK) y modifique su respuesta anterior.)

De estos hombres...

20_1. ¿cuántos realmente le dijeron a usted que eran VIH negativos y usted no tuvo razones para dudarlos?

20_2. ¿cuántos sabe usted que son VIH positivos?

20_3. ¿de cuántos no estaba usted completamente segura del estado de VIH?

SI P 11 = 0, OMITA LAS P 22 - 24

22. Ahora quisiera preguntarle sobre sexo anal receptivo. Recuerde, al decir sexo anal receptivo, me refiero a cuando un hombre o muchacho introduce su pene dentro de su ano o nalgas. Durante los últimos 90 días, ¿tuvo usted sexo anal receptivo con alguna pareja masculina?

0. No

1. Sí

22a. ¿Cuántas parejas masculinas introdujeron su pene en su ano o nalgas durante los últimos 90 días?

23a. ¿En cuántas ocasiones introdujo una pareja masculina su pene dentro de su ano o nalgas durante los últimos 90 días, esto es desde [DATE]?

23b. ¿En cuántas ocasiones introdujo una pareja su pene dentro de su ano o nalgas sin condón durante los últimos 90 días?

24. ¿Cuántas parejas masculinas diferentes introdujeron su pene en su ano o nalgas sin condón durante los últimos 90 días?

IF Q 24 > 1 (i.e., THE PARTICIPANT REPORTS THAT MORE THAN ONE MAN PENETRATED HER VAGINA WITHOUT A CONDOM), SKIP TO Q 24b. IF Q 24 = 1, ASK Q 24a AND SKIP Q 25

Usted dijo que una pareja introdujo su pene en su ano o nalgas sin condón.

24a. En relación con esta pareja (por favor seleccione una respuesta).....

___ a. Esta pareja le dijo que era VIH negativo y usted no tenía razón para dudarlos.

___ b. Usted sabía que esta pareja era VIH positivo.

___ c. Usted no estaba completamente segura del estado de VIH de esta pareja.

Usted dijo que ___ hombres **[INSERT THE NUMBER FROM Q 24]** introdujeron su pene en su ano o nalgas sin condón. (Si este número es incorrecto, por favor haga clic en el botón "ATRÁS" (BACK) y modifique su respuesta anterior.)

De estos hombres...

24b_1. ¿cuántos realmente le dijeron a usted que eran VIH negativos y usted no tuvo razones para dudarlo?

24b_2. ¿cuántos sabe usted que son VIH positivos?

24b_3. ¿de cuántos no estaba usted completamente segura de su estado de VIH?

25. Pensando aún en los últimos 90 días, quiero hacerle algunas preguntas sobre todas las parejas masculinas con las que tuvo sexo, ya sea vaginal o anal, durante dicho período. Primero, durante los últimos 90 días, ¿alguna vez le pidió a una pareja que utilizara condón?

0. No

1. Sí

SI P 25 = 0, VAYA A LA P 27

26. ¿Alguna de sus parejas se rehusó a utilizar condón cuando usted se lo pidió?

0. No

1. Sí

SI P 12 = 0, OMITA LA P 27

27. Ahora quiero preguntarle respecto a dar sexo oral. Recuerde, al decir dar sexo oral, me refiero a cuando usted coloca su boca o lengua en el pene, vagina o ano (o nalgas) de su pareja. Durante los últimos 90 días, ¿usted dio sexo oral a alguna de sus parejas, ya sea femenina o masculina?

0. No

1. Sí

SI P 13 = 0, OMITA LA P 28 Y VAYA A LAS INSTRUCCIONES ANTES DE LA P 29

28. Ahora quiero preguntarle respecto a recibir sexo oral. Recuerde, al decir recibir sexo oral, me refiero a cuando su pareja coloca su boca o lengua en su vagina o ano (o nalgas). Durante los últimos 90 días, ¿usted recibió sexo oral de alguna de sus parejas?

0. No

1. Sí

INFORMACIÓN DE LA PAREJA

La siguiente serie de preguntas es sobre su(s) más reciente(s) pareja(s) sexual(es). Se le harán algunas preguntas sobre estas parejas. Revisemos brevemente las definiciones de algunos términos para que usted entienda lo que se le pregunta.

Una pareja masculina principal es alguien con quien usted tiene sexo y que usted considera que es una persona con la que tiene una relación seria. Una pareja principal es alguien con quien usted tiene una relación actual y con quien usted tiene sexo frecuentemente – tal como un esposo, amante o novio.

Una pareja masculina casual es alguien con quien usted tiene sexo dos o más

veces pero que no considera ser una persona que sea una pareja principal. Una pareja casual es alguien con quien usted tiene sexo ocasionalmente en forma casual.

Una pareja masculina de una ocasión es alguien con quien usted ha tenido sexo una vez y con quien no planea tener sexo nuevamente.

29. ¿Cuántas parejas masculinas principales ha tenido en los últimos 90 días? Si no tuvo una pareja principal, ponga "0" como respuesta.

30. ¿Cuántas parejas masculinas casuales ha tenido en los últimos 90 días? Si no tuvo una pareja casual, ponga "0" como respuesta.

31. ¿Cuántas parejas masculinas de una ocasión tuvo en los últimos 90 días? Si no tuvo una pareja de una ocasión, ponga "0" como respuesta.

32. Pensando en la persona masculina con la que ha tenido relaciones sexuales más recientemente, esta pareja es:

1. Una pareja principal
2. Una pareja casual
3. Una pareja de una ocasión

SE HARÁN LAS SIGUIENTES PREGUNTAS PARA LA PAREJA PRINCIPAL MÁS RECIENTE. SI P 29 = 0, OMITA LAS P 33 HASTA LA P 39.

PAREJA PRINCIPAL

Usted indicó que actualmente tiene o que, en los últimos 90 días ha tenido una pareja principal. La siguiente serie de preguntas se referirán a su pareja masculina principal más reciente.

33. ¿Qué edad tiene o qué edad tenía esta pareja principal más reciente en el momento en que ustedes estaban juntos?

EDAD

No Sabe/No está segura.....999

ACCEPTABLE AGE RANGE IS 01-99. IF RANGE FAILURE, SHOW PROMPT THAT READS, "Quiero confirmar la edad de su pareja principal más reciente. Usted ha escrito _____. ¿Es esto correcto? IF AGE ENTERED IS 0 SHOW PROMPT THAT READS, "Usted ha escrito una edad no válida. Por favor escriba de nuevo." ALSO ADD A SOFT RANGE CHECK TO CONFIRM ANY AGES <10 OR >40.

34. ¿Cuál es el antecedente racial/étnico de esta pareja más reciente

- ___ 1. Asiático/Nativo de Islas del Pacífico
- ___ 2. Negro/ Afro americano
- ___ 3. Americano Nativo/ Nativo de Alaska
- ___ 4. Hispano/Latino
- ___ 5. Blanco
- ___ 6. Otro o mezcla étnica

35. ¿Cuántas veces tuvo sexo, ya sea vaginal o anal, con esta pareja principal más reciente durante los últimos 90 días?

FIELD SHOULD ALLOW A FOUR-DIGIT NUMBER, BUT PROGRAM A SOFT RANGE CHECK WITH RANGE FAILURE FOR ANY RESPONSE OVER 300. IF RANGE FAILURE, SHOW PROMPT THAT READS, "Quiero confirmar el número de veces que tuvo sexo, ya sea vaginal o anal, con esta pareja principal más reciente. Usted escribió _____. ¿Es esto correcto?"

36. De estas [INSERT NUMBER FROM Q35 ABOVE] veces, ¿cuántas veces utilizó un condón con esta pareja principal más reciente?

37. La última vez que usted tuvo sexo con esta pareja principal más reciente, ¿qué utilizó usted para prevenir un embarazo? Marque todas las que correspondan.

- ___ 1. Condón
- ___ 2. Píldora
- ___ 3. Inyección de Depo-Provera
- ___ 4. Norplant o Implanon
- ___ 5. Coito interrumpido
- ___ 6. Parcho (Ortho Evra)
- ___ 7. Anillo vaginal (Nuva Ring)
- ___ 8. El ritmo
- ___ 9. DIU (por ejemplo, Mirena® o T de Cobre)
- ___ 10. Nada
- ___ 11. Otros

38. ¿Le preguntó a esta pareja principal más reciente si se había hecho pruebas de VIH, o esta pareja le dijo a usted que se había hecho pruebas de VIH?

- 0. No
- 1. Sí

SI P 38 = 0, OMITA LA P 39

39. ¿Cuál fue el resultado de la prueba de su pareja?

- ___ 1. VIH positivo
- ___ 2. VIH negativo
- ___ 3. La pareja no me dijo los resultados
- ___ 4. La pareja no recogió los resultados

SECCIÓN C. DUCHAS, LUBRICANTES Y OTROS PRODUCTOS VAGINALES (Name of products will be tailored to study site)

La siguiente serie de preguntas es sobre productos vaginales.

40. ¿Alguna vez ha utilizado un tampón?
0. No [VAYA A LA P 42]
1. Sí
41. ¿Ha utilizado tampón con aplicador, sin aplicador o ambos?
a. con aplicador
b. sin aplicador
c. ambos
42. ¿Alguna vez ha utilizado una diafragma/cervical cap?
0. No
1. Sí

Por favor indique si ha utilizado alguna vez alguno de los siguientes productos:

43. Desecantes, esto es, cualquier cosa que haga que su vagina se seque o se endurezca, tal como Tight Stuff
0. No
1. Sí
44. Condones femeninos, también llamados "Reality®"
0. No
1. Sí
45. Lubricantes vaginales o lubricantes sexuales, tales como Lubrin, Replens, Moist Again, o KY en jalea (gel) o líquido
0. No
1. Sí
46. Medicamentos para infecciones vaginales por hongos que usted aplique en su vagina tales como Femstat o Gyne-Lotrimin
0. No
1. Sí
47. Espermicidas, esto es, una espuma, gel, membrana, supositorio o crema que mate espermatozoides y que prevenga el embarazo
0. No
1. Sí

Las siguientes preguntas se refieren al uso de duchas vaginales.

48. ¿Ha utilizado alguna vez una ducha vaginal? Al decir ducha vaginal nos referimos a algo que usted utilice para rociar un líquido dentro de su vagina.
0. No [VAYA A LA SIGUIENTE SECCIÓN (P 52)]
1. Sí

49. ¿Cuántas veces utilizó duchas vaginales en los últimos 3 (tres) meses?

___ ___ ___ [SI '0,' VAYA A LA SIGUIENTE SECCIÓN (P 52)] [0-999]

50. De las veces que utilizó duchas vaginales en los últimos 3 meses, ¿cuántas veces utilizó duchas vaginales... [Marque todas las que correspondan] [1-999]

- a. por higiene personal? ___ ___
- b. en preparación para el sexo? ___ ___
- c. después del sexo? ___ ___
- d. por placer? ___ ___
- e. cuando terminó su período menstrual? ___ ___
- f. mientras tenía su período menstrual? ___ ___
- g. por tener comezón/picor en la vagina o sentirse incómoda? ___ ___
- h. por otras razones? ___ ___

51. Cuando utilizó duchas vaginales en los últimos 3 (tres) meses, ¿cuántas veces utilizó...[Marque todas las que correspondan] [1-999]

- a. Una manguera manual o bidet? ___ ___
 - b. Un producto de ducha desechable sin receta?
(por ejemplo, Massengill® o Summer's Eve®) ___ ___
 - c. Un sistema de botella re-utilizable? ___ ___
 - d. Agua y vinagre? ___ ___
 - e. Otros? ___ ___
-

SECCIÓN D. USO DE LUBRICANTES PARA EL SEXO

Las siguientes preguntas se refieren a lubricantes sexuales comerciales. Esto no incluye saliva ni el lubricante que viene con los condones, sino que se refiere al lubricante que usted compra sin receta o en una tienda.

52. ¿Ha utilizado un lubricante comercial durante el sexo vaginal?
0. No [VAYA A LA P 66]
1. Sí
53. Durante los últimos 3 meses, ¿con cuánta frecuencia ha tenido sexo vaginal utilizando un lubricante sexual comercial?
_____ 0 Nunca [VAYA A LA P 66]
_____ 1 A veces
_____ 2 Siempre
54. ¿Qué tipo de lubricante ha usado? [Marque todas las que correspondan]
_____ 1 A base de silicona (ejemplo, Eros)
_____ 2 A base de agua (ejemplo, KY, Wet)
_____ 3 A base de aceite (ejemplo, Crisco)
55. ¿Dónde obtiene generalmente su lubricante?
_____ 1 Tienda sexual
_____ 2 Farmacia/botica
_____ 3 Agencia de SIDA
_____ 4 Bar, disco, club sexual
_____ 5 En la red
_____ 6 Otro
56. ¿Prefiere usted un lubricante con...
_____ 0 Ningún sabor
_____ 1 Sabor
_____ 2 No importa
57. ¿Prefiere usted un lubricante con ...
_____ 0 Ningún color/transparente
_____ 1 Color
_____ 2 No importa
58. ¿Prefiere usted un lubricante con ...
_____ 0 Ningún olor
_____ 1 Olor
_____ 2 No importa
59. En relación con la consistencia del lubricante comercial, ¿qué prefiere usted?
0 1 2 3 4
•—————•—————•—————•—————•
Muy Algo líquido Ni líquido ni Algo espeso Muy
líquido líquido espeso espeso espeso

60. Describa el tipo ideal de contenedor (envase) para un lubricante.
- 1 Tubo (como pasta de dientes o KY®)
 - 2 De bombeo (como en Vaseline Intensive Care® o Wet®)
 - 3 Contenedores con cubiertas pop-up
 - 4 Lata o frasco
 - 5 De un solo uso
 - 6 Tubo desechable
 - 7 Otro
61. Por lo general, cuándo usted tiene sexo vaginal, ¿el lubricante se aplica...[Indique todas las que apliquen]
- 1 directamente en el pene de su pareja?
 - 2 en el exterior de su vagina?
 - 3 dentro de su vagina?
 - 4 dentro del condón?
 - 5 en el exterior del condón?
 - 6 Otro
62. Cuando tiene sexo vaginal, ¿quién aplica el lubricante?
- 0 Yo
 - 1 Pareja
 - 2 Ambos
63. ¿Cuándo usa el lubricante por primera vez?
- 0 Antes de cualquier contacto sexual
 - 1 Durante el sexo pero antes de que él la penetre a usted
 - 2 Después de que él la penetre si usted siente necesidad
64. ¿Con cuánta frecuencia usted vuelve a aplicar el lubricante comercial durante el sexo vaginal?
- 0 Nunca
 - 1 Una vez
 - 2 Dos veces
 - 3 3 veces o más
65. De su experiencia en el pasado, ¿la aplicación del lubricante interrumpe el acto sexual?
- 0 No interrumpe el acto sexual
 - 1 Interrumpe el acto sexual pero no me molesta
 - 2 Interrumpe el acto sexual y me molesta

SI P11 = 0 (NUNCA HA TENIDO SEXO ANAL), VAYA A LA SIGUIENTE SECCIÓN (P 72).

66. ¿Alguna vez ha utilizado un lubricante comercial durante el sexo anal?
- 0. No [VAYA A LA SIGUIENTE SECCIÓN (P 72)]
 - 1. Sí

67. ¿Qué tipo de lubricante ha usado? [Marque todas las que correspondan]
- 1 A base de silicona (ejemplo, Eros)
 - 2 A base de agua (ejemplo, KY, Wet)
 - 3 A base de aceite (ejemplo, Crisco)
68. Describa el tipo ideal de contenedor para un lubricante.
- 1 Tubo (como pasta de dientes o KY®)
 - 2 De bombeo (como en Vaseline Intensive Care® o Wet®)
 - 3 Contenedores con cubiertas pop-up
 - 4 Lata o frasco
 - 5 De un solo uso
 - 6 Tubo desechable
 - 7 Otro
69. Por lo general, cuando usted tiene sexo anal, ¿el lubricante se aplica...[Indique todas las que apliquen]
- 1 directamente en el pene de su pareja?
 - 2 alrededor de su ano?
 - 3 dentro de su ano?
 - 4 dentro del condón?
 - 5 en el exterior del condón?
 - 6 Otro
70. Cuando tiene sexo anal, ¿quién aplica el lubricante?
- 0 Yo
 - 1 Pareja
 - 2 Ambos
71. ¿Cuándo usa el lubricante por primera vez?
- 0 Antes de cualquier contacto sexual
 - 1 Durante el sexo pero antes de que él la penetre a usted
 - 2 Después de que él la penetre si usted siente necesidad
-

SECCIÓN E. HISTORIAL DE PRUEBAS DE VIH & USO DE SUSTANCIAS

Las siguientes preguntas se refieren al uso de alcohol y drogas (fármacos). Ahora le mostraré una lista de distintas drogas.

[PRIMERO OBSERVE LA COLUMNA "A". SI LA RESPUESTA PARA CUALQUIER SUSTANCIA ES "0", OMITA LA COLUMNA "B" PARA ESA SUSTANCIA EN PARTICULAR.] USE LAS SIGUIENTES OPCIONES DE RESPUESTA:

- 0 = Nunca/ninguna
- 1 = Una vez al mes o menos
- 2 = 2-3 veces al mes
- 3 = Alrededor de una vez a la semana
- 4 = 2-6 veces a la semana
- 5 = Alrededor de una vez al día
- 6 = Más de una vez al día

- A. Durante los últimos 90 días, ¿con cuánta frecuencia ha usted utilizado [INSERTE SUSTANCIA]
- B. De estas veces durante los últimos 90 días, ¿con cuánta frecuencia ha usted utilizado [INSERTE SUSTANCIA] inmediatamente antes o durante las relaciones sexuales?

	[A] Número de veces que utilizó en los ÚLTIMOS 3 MESES	[B] Número de veces que utilizó antes o durante el SEXO EN LOS ÚLTIMOS 3 MESES
72. Alcohol (cerveza, vino, licor)?		
73. Marihuana/hashish/Hierba/?		
74. Éxtasis/MDMA?		
75. Metanfetamina Cristal/Anfetaminas/ Metanfetaminas/Speed/Crack/Ice?		
76. Ketamina/Special K?		
77. GHB (Gamma Hidroxibutirato)?		
78. Otros alucinógenos/LSD/ Hongos?		
79. Poppers/Amil-Nitrato/Butil-Nitrato?		
80. Crack?		
81. Cocaína (no Crack)?		
82. Heroína?		
83. DELETED		

84. Otros fármacos de farmacia no recetados para usted por su médico (Percocet o fármacos similares)?		
---	--	--

85. Pensando en las veces en las que usted tomó bebidas alcohólicas durante los últimos 90 días, ¿cuánto utilizó generalmente?

___ 0. Muy poco para sentir efectos

___ 1. Suficiente para sentirlo un poco

___ 2. Suficiente para sentirlo mucho

___ 3. Suficiente para emborracharse

___ 4. Suficiente para hacerle sentir que podría perder el sentido

86. En total, ¿cuántas veces se ha hecho la prueba del VIH? Si nunca lo ha hecho, escriba 0.

SECCIÓN F. PROBABILIDAD DE UTILIZAR UN MICROBICIDA EN EL FUTURO

Los científicos están tratando de desarrollar alternativas al condón para la prevención del VIH durante el sexo. En este estudio, estamos interesados en gel y enemas o duchas.

87. Si estuviera disponible un microbicida vaginal que proporcionara cierta protección contra el VIH y fuera un gel, ¿qué tan probable sería que usted lo utilizara cada vez que tenga sexo vaginal?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Muy Improbable Muy Probable

88. Si estuviera disponible un microbicida rectal que proporcionara cierta protección contra el VIH, y fuera un gel, ¿qué tan probable sería que usted lo utilizara cada vez que tenga sexo anal?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Muy Improbable Muy probable

89. Si el uso de una ducha vaginal antes de las relaciones sexuales proporcionara cierta protección contra el VIH, ¿qué tan probable sería que usted se aplicara una ducha vaginal antes de cada ocasión en que usted tenga relaciones sexuales vaginales?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Muy Improbable Muy probable

90. Si el uso de un enema antes de tener sexo anal proporcionara cierta protección contra el VIH, ¿qué tan probable sería que usted se aplicara un enema antes de cada ocasión en que usted tenga sexo anal?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Muy Improbable Muy Probable

SECCIÓN G. PLACER

Por favor lea los siguientes comportamientos sexuales e indique **cuánto le gustaría practicar cada comportamiento con HOMBRES si no existiera el SIDA**. Por favor conteste cada pregunta sin importar si alguna vez lo ha hecho o si planea hacerlo en un futuro.

	Me disgustaría mucho	Me disgustaría algo	Me disgustaría un poco	Me gustaría un poco	Me gustaría algo	Me gustaría mucho
91. Tener sexo vaginal SIN condón	1	2	3	4	5	6
92. Tener sexo vaginal CON condón	1	2	3	4	5	6
93. Que su pareja eyacule dentro de su vagina SIN un condón	1	2	3	4	5	6

Por favor indique:

94. ¿Cuánto interfieren los condones con su satisfacción sexual cuando es penetrada vaginalmente?

1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10
 Para nada Mucho

SI la P11 = 0 NUNCA HA TENIDO SEXO ANAL), OMITA LAS P 95 - 98 y ESTE ES EL FIN DEL CUESTIONARIO. "Se ha completado la entrevista. Muchas gracias."

Por favor indique **cuánto le gustaría practicar cada comportamiento con HOMBRES si no existiera el SIDA**. Por favor conteste cada pregunta sin importar si alguna vez lo ha hecho o si planea hacerlo en un futuro. [ALLOW ONLY ONE ANSWER PER QUESTION.]

	Me disgustaría mucho	Me disgustaría algo	Me disgustaría un poco	Me gustaría un poco	Me gustaría algo	Me gustaría mucho
95. Tener sexo anal SIN condón	1	2	3	4	5	6
96. Tener sexo anal CON condón	1	2	3	4	5	6
97. Que su pareja eyacule dentro de su recto SIN un condón	1	2	3	4	5	6

98. ¿Cuánto interfieren los condones con su satisfacción sexual cuando es penetrada por el ano?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Para nada Mucho

Se ha completado la entrevista. Muchas gracias

Sección II

SECCIÓN A. ACEPTACIÓN DEL PRODUCTO

1. En general (esto es, considerando todos los episodios en los que utilizó este gel), ¿qué tanto le gusto el gel?

1—2—3—4—5—6—7—8—9—10
Me disgustó Ni me gustó ni Me gustó
mucho me disgustó Mucho

2. ¿Qué tanto le gustó el color del gel?

1—2—3—4—5—6—7—8—9—10
Me disgustó Ni me gustó ni Me gustó
mucho me disgustó Mucho

3. ¿Qué tanto le gusto el sabor del gel?

[99] No sé, no probé el gel

1—2—3—4—5—6—7—8—9—10
Me disgustó Ni me gustó ni Me gustó
mucho me disgustó Mucho

4. ¿Qué tanto le gustó el olor del gel?

[99] No sé, no olí el gel

1—2—3—4—5—6—7—8—9—10
Me disgustó Ni me gustó ni Me gustó
mucho me disgustó Mucho

5. ¿Cuánto le gustó la consistencia del gel (lo espeso o diluido que era)?

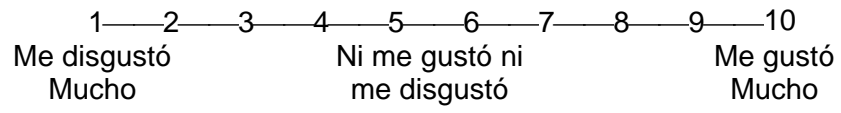
1—2—3—4—5—6—7—8—9—10
Me disgustó Ni me gustó ni Me gustó
mucho me disgustó Mucho

6. ¿Qué tanto le gusto la sensación del gel dentro de su vagina inmediatamente después de insertarlo?

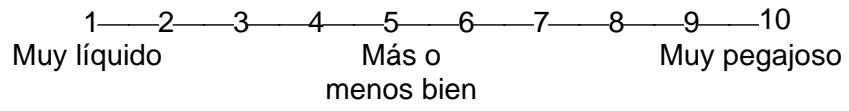
1—2—3—4—5—6—7—8—9—10
Me disgustó Ni me gustó ni Me gustó
mucho me disgustó Mucho

7. ¿Qué tanto le gustó la sensación del gel dentro de su vagina 30 minutos después de haberlo insertado?

[99] No sé, no tuve el gel dentro de mi vagina por 30 minutos.



8. El gel se sintió..



SECCIÓN B. ADHERENCIA AL PRODUCTO

9. Se le pidió que insertara el gel en su vagina dos veces al día durante 14 días. Sin embargo, diversas circunstancias pueden haberle impedido que lo hiciera todas las veces. Por favor indique el número total de veces que usted utilizó el gel durante el período de estudio.

_____ [rango 0 – 30]

10. Por favor marque todas las que correspondan en caso de que cualquiera de las siguientes razones le impidiera utilizar el gel.

- Se me olvidó
 - No tenía el gel conmigo
 - Mi pareja sexual no quería que yo utilizara el gel
 - No me gustó la sensación del gel dentro de mí
 - Tuve sangrado vaginal y decidí dejar de utilizar el gel
 - Empecé con mi regla
 - Tuve una sensación de ardor al utilizar el gel
 - Tuve una sensación de comezón al utilizar el gel
 - El gel goteaba todo el tiempo
 - El gel ensuciaba demasiado
 - No quería utilizar el gel
 - Otro
-

SECCIÓN C. PROCESO DE APLICACIÓN

11. En general, ¿qué tanto le gusto poner el gel dentro de su vagina?

1—2—3—4—5—6—7—8—9—10
Me disgustó Ni me gustó ni Me gustó
Mucho me disgustó Mucho

12. ¿Qué tan sencillo fue poner el gel dentro de su vagina?

1— 2— 3— 4—5—6—7—8—9—10
Muy Ni fácil ni Muy
Difícil difícil Fácil

13. ¿En dónde estaba usted cuando puso el gel dentro de su vagina? (Marque todas las que correspondan.)

1. Baño
2. Recámara
3. Otro

14. ¿Qué posición utilizó habitualmente para poner el gel dentro de su vagina? [CASI ALLOW ONLY ONE ANSWER.]

1. Arrodillada
 2. Acostada sobre un costado
 3. Parada
 4. De cuclillas o sentada sobre el escusado o la tina
 5. Otro
-

SECCIÓN D. APLICADOR

15. ¿Qué tanto le gustó el aplicador del gel (el instrumento que utilizó para liberar el gel dentro de su vagina)?

1—2—3—4—5—6—7—8—9—10
Me disgustó mucho Ni me gustó ni me disgustó Me gustó Mucho

16. ¿Tuvo algún problema con el aplicador utilizado para liberar el gel en su vagina?

- 0. No
- 1. Sí

17. ¿Qué tan fácil sería llevar este gel con usted si lo necesitara?

1—2—3—4—5—6—7—8—9—10
Extremadamente Difícil Ni fácil ni difícil Extremadamente Fácil

18. ¿Qué tan fácil sería para usted almacenar este gel?

1—2—3—4—5—6—7—8—9—10
Extremadamente Difícil Ni fácil ni difícil Extremadamente Fácil

19. ¿Qué tan preocupada estaría usted si alguien descubriera que tiene este gel almacenado?

1—2—3—4—5—6—7—8—9—10
Extremadamente Preocupada No me preocuparía para nada

SECCIÓN E. CAMBIOS EN LA CANTIDAD USADA

20. ¿Alguna vez utilizó menos de la cantidad total de gel que venía en cada aplicador?
[0] No [VAYA A LA SIGUIENTE SECCIÓN]
[1] Sí
21. De ser así, ¿en cuántas ocasiones utilizó menos de la cantidad total de gel?
[1] 1 de las ocasiones
[2] 2 de las ocasiones
[3] En 3 o más de las ocasiones
22. Cuando utilizó menos de la cantidad total, ¿cuánto utilizó, en promedio?
[1] Tres cuartas partes de la dosis
[2] La mitad de la dosis
[3] Una cuarta parte de la dosis
23. Por favor indique la razón por la que utilizó menos de la cantidad total de gel
(marque todas las que correspondan)
[1] Ensuciaba demasiado
[2] Se escurría
[3] Temía que pudiera ser malo para mí
[4] Tuve problemas para utilizar el aplicador
[5] Otro
-

SECCIÓN F. EXPERIENCIAS AL UTILIZAR EL PRODUCTO

24. ¿Tuvo algún problema al utilizar este gel?

[0] No

[1] Sí

25. ¿Tuvo algún goteo o pérdida de gel después de utilizarlo?

[0] No [VAYA A LA P 27]

[1] Poco

[2] Mucho

26. ¿Qué tanto le molestó el goteo o pérdida?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Para Mucho
nada

27. ¿Notó alguna vez goteo o pérdida en su ropa interior o sábanas de la cama?

[0] No [VAYA A LA SIGUIENTE SECCIÓN (P 29)]

[1] Poco

[2] Mucho

28. ¿Qué tanto le molestó el goteo o pérdida del gel en la ropa interior o sábanas de la cama?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Para Mucho
nada

SECCIÓN G. RELACIONES SEXUALES USANDO EL PRODUCTO

Durante este estudio...

29. ¿Con cuántas parejas masculinas tuvo sexo vaginal? ____
Al decir sexo vaginal, nos referimos a cuando un hombre o muchacho introduce su pene en su vagina.

SI LA P 29 = 0, OMITA LAS P 30 - 34 Y VAYA A LA P 35.

30. ¿Cuántas veces tuvo sexo vaginal? ____

31. ¿Cuántas veces tuvo sexo vaginal utilizando el gel con condones? ____

32a. ¿Cuántas veces tuvo sexo vaginal utilizando el gel sin condones? ____

32b. ¿Cuántas veces tuvo sexo vaginal utilizando condones sin el gel?

33. ¿Cuántas veces tuvo sexo vaginal sin utilizar ni el gel ni condones? ____

34. ¿Con cuántas parejas utilizó el gel durante el sexo vaginal? ____

NUMBER OF PARTNERS MUST BE <= RESPONSE GIVEN IN Q 29. IF Q 34 > Q 29, SHOW PROMPT, "Usted indicó que tuvo sexo vaginal con XX número de parejas durante este estudio. Sin embargo, acaba de indicar que utilizó el gel durante el sexo vaginal con XX número de parejas. Si esto es incorrecto, por favor vuelva a escribir su respuesta. En caso contrario, vuelva a la pregunta # 29 para corregir su respuesta a esa pregunta."

Durante este estudio...

35. ¿Con cuántas parejas masculinas tuvo sexo anal? ____
Al decir sexo anal, nos referimos a cuando un hombre o muchacho introduce su pene en su ano (o nalgas).

SI LA P 35 = 0, OMITA LAS P 36 - 40 Y VAYA A LA SIGUIENTE SECCIÓN (P 41).

36. ¿Cuántas veces tuvo sexo anal? ____

37. ¿Cuántas veces tuvo sexo anal utilizando el gel en su ano o recto (o nalgas) junto con condones? ____

38a. ¿Cuántas veces tuvo sexo anal utilizando el gel en su ano o recto (o nalgas) sin utilizar condones? ____

38b. ¿Cuántas veces tuvo sexo anal utilizando condones sin el gel en su ano o recto (o nalgas)?

39. ¿Cuántas veces tuvo sexo anal sin utilizar ni gel ni condones? ____

40. ¿Con cuántas parejas utilizó el gel durante el sexo anal? ____

NUMBER OF PARTNERS MUST BE <= RESPONSE GIVEN IN Q 35. IF Q 40 > Q 35, SHOW PROMPT, "Usted indicó que tuvo sexo anal con XX número de parejas durante este estudio. Sin embargo, acaba de indicar que utilizó el gel durante el sexo anal con XX número de parejas. Si esto es incorrecto, por favor vuelva a escribir su respuesta. En caso contrario, vuelva a la pregunta # 35 para corregir su respuesta a esa pregunta."

SECCIÓN H. REACCIÓN DE LA PAREJA

Permítanos recordarle a qué nos referimos al decir pareja principal, casual y de una ocasión.

Una pareja masculina principal es alguien con quien usted tiene sexo y que usted considera que es una persona con la que tiene una relación seria. Una pareja principal es alguien con quien usted tiene una relación actual y con quien usted tiene sexo frecuentemente – tal como un esposo, amante o novio.

Una pareja masculina casual es alguien con quien usted tiene sexo dos o más veces pero que no considera ser una persona que sea una pareja principal. Una pareja casual es alguien con quien usted tiene sexo ocasionalmente en forma casual.

Una pareja masculina de una ocasión es alguien con quien usted ha tenido sexo una vez y con quien no planea tener sexo nuevamente.

41. ¿Con qué tipo de pareja utilizó el gel durante las relaciones vaginales o anales? Marque todas las que correspondan.

- 1. Pareja principal
- 2. Pareja casual
- 3. Pareja de una ocasión

42. ¿Alguna de sus parejas supo que usted utilizó este gel?

[0] No [OMITA LA P 43, VAYA A LAS INSTRUCCIONES ANTERIORES A LA P 44]

[1] Sí

43. ¿Qué tipo de pareja supo que usted había utilizado este gel? Marque todas las que correspondan.

- 1. Pareja(s) principal(es)
- 2. Pareja(s) casual(es)
- 3. Pareja(s) de una ocasión

SI EN LA P 41 NO SE SELECCIONA LA ALTERNATIVA 1 (PAREJA PRINCIPAL), OMITA LA P 44 Y VAYA A LAS INSTRUCCIONES ANTERIORES A LA P 45.

44. En general, ¿cuánto le gustó a su pareja principal más reciente el gel?

[99] No sé

1—2—3—4—5—6—7—8—9—10
No le gustó Ni le gustó ni Le gustó
para nada le disgustó mucho

SI EN LA P 41 NO SE SELECCIONA LA ALTERNATIVA 2 (PAREJA CASUAL), OMITA LA P 45 Y VAYA A LAS INSTRUCCIONES ANTERIORES A LA P 46.

45. En general, ¿cuánto le gustó a su pareja casual más reciente el gel?

[99] No sé

1—2—3—4—5—6—7—8—9—10
No le gustó Ni le gustó ni Le gustó
para nada le disgustó mucho

SI EN LA P 41 NO SE SELECCIONA LA ALTERNATIVA 3 (PAREJA DE UNA OCASIÓN),
OMITA LA P 46 Y VAYA A LA SIGUIENTE SECCIÓN(P 47).

46. En general, ¿cuánto le gustó a su pareja de una ocasión más reciente elgel?

[99] No sé

1—2—3—4—5—6—7—8—9—10
No le gustó Ni le gustó ni Le gustó
para nada le disgustó Mucho

SECCIÓN I. PLACER SEXUAL DESPUÉS DEL USO DEL PRODUCTO

47. ¿Cuánto le gustó el sexo vaginal cuando utilizó elgel?

1—— 2—— 3—— 4——5——6——7——8——9——10
Me disgustó Ni me gustó ni Me gustó
mucho me disgustó Mucho

48. En general, ¿qué tan sexualmente satisfecha estuvo con el sexo vaginal cuando utilizó elgel?

1—— 2—— 3—— 4——5——6——7——8——9——10
Para Mucho
nada

49. En general, ¿qué tan sexualmente satisfecha cree usted que estuvo su pareja cuando usted utilizó elgel? (Si usted utilizó el gel con más de una pareja, refiérase únicamente a su pareja sexual más reciente.)

1—— 2—— 3—— 4——5——6——7——8——9——10
Para Mucho
nada

50. ¿Qué tan sexualmente satisfecha se siente usted con esta pareja en general cuando tiene sexo vaginal y NO utiliza este gel de estudio?

[88] No aplica, únicamente he tenido sexo con esta pareja utilizando el gel de estudio

1—— 2—— 3—— 4——5——6——7——8——9——10
Para Mucho
nada

SECCIÓN J. CONDONES

51. ¿Cuánto le gusto tener relaciones sexuales con condones después de insertar el gel?

1—2—3—4—5—6—7—8—9—10
No me gustó Ni me gustó ni Me gustó
nada me disgustó Mucho

52. ¿Cuánto le gusto tener relaciones sexuales sin condón después de insertar el gel?

1—2—3—4—5—6—7—8—9—10
No me gustó Ni me gustó ni Me gustó
nada me disgustó Mucho

SECCION K. CAMBIOS EN PRÁCTICAS SEXUALES DEBIDOS AL USO DEL PRODUCTO

53. Pensando en su experiencia al tener sexo vaginal después de utilizar este gel en específico, ¿esta fue mejor, peor o no hubo diferencia alguna respecto a otras ocasiones en las que no utilizó este gel?

- [2] Mejor
- [1] Peor
- [0] No hubo diferencia [VAYA A LA P55]

54. Después de utilizar el gel, ¿fue más fácil la penetración vaginal?

- [0] No
- [1] Sí, la penetración fue un poco más fácil
- [2] Sí, la penetración fue mucho más fácil

55. ¿Alguna vez tuvo que interrumpir el sexo para aplicar el gel?

- [0] No [VAYA A LA SIGUIENTE SECCIÓN]
- [1] Sí

56. ¿Qué tanto le molestó haber tenido que interrumpir el sexo para aplicar el gel?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Para Mucho
Nada

SECCIÓN L. PROBABILIDAD DE UTILIZAR EL PRODUCTO EN UN FUTURO

GEL

57. Si estuviera disponible un gel que proporcionara cierta protección contra el VIH, y se pareciera al que usted utilizó en este estudio, ¿qué tan probable sería que usted lo utilizara cada vez que tenga sexo vaginal?

1—— 2—— 3—— 4——5——6——7——8——9——10
Muy Ni probable Muy
improbable ni improbable probable

58. ¿Qué tan probable sería que usted utilizara un gel que proporcionara cierta protección contra el VIH en las ocasiones en las que usted no utiliza condones?

1—— 2—— 3—— 4——5——6——7——8——9——10
Muy Ni probable Muy
improbable ni improbable probable

59. ¿Qué tan probable sería que usted utilizara un gel si tuviera que esperar 30 minutos después de la aplicación para tener relaciones sexuales?

1—— 2—— 3—— 4——5——6——7——8——9——10
Muy Ni probable Muy
improbable ni improbable probable

60. ¿Cuánto estaría dispuesto a gastar en un gel en cada encuentro sexual?

1. La mitad de lo que gasto en condones
2. Aproximadamente lo mismo que gasto en condones
3. El doble de lo que gasto en condones
4. Tres veces lo que gasto en condones
5. Nada. Solo utilizaría el gel si lo recibiera gratis
6. Otro

SECCIÓN M. DISPOSICIÓN PARA UTILIZAR UN MAYOR VOLUMEN

Ahora, no sabemos aún el volumen de este gel que sería necesario para ayudar a protegerla contra el VIH durante el sexo.

61a. Pensando en la cantidad de gel que utilizó, ¿qué tan probable sería que lo utilizara cada vez que tenga sexo vaginal si la misma cantidad fuera necesaria?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Muy Ni probable Muy
Improbable ni improbable probable

61b. Pensando en la cantidad de gel que utilizó, ¿qué tan probable sería que lo utilizara cada vez que tenga sexo vaginal si sólo la mitad fuera necesaria?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Muy Ni probable Muy
Improbable ni improbable probable

62. ¿Qué tan probable sería que utilizara el gel cada vez que tenga sexo vaginal si fuera necesario utilizar el doble?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Muy Ni probable Muy
improbable ni improbable probable

SECCIÓN N. POSIBILIDAD DE USO ENCUBIERTO

63. ¿Querría usted utilizar este gel sin el conocimiento de su pareja principal?

[0] No

[1] Sí

64. Según su opinión ¿qué tan probable sería que su pareja masculina principal notara el gel durante las relaciones sexuales?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Muy Ni probable Muy
improbable ni improbable probable

65. Según su opinión ¿qué tan probable sería que su pareja masculina casual notara el gel durante las relaciones sexuales?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Muy Ni probable Muy
improbable ni improbable probable

66. Según su opinión ¿qué tan probable sería que su pareja masculina de una ocasión notara el gel durante las relaciones sexuales?

1—— 2—— 3—— 4—— 5—— 6—— 7—— 8—— 9—— 10
Muy Ni probable Muy
Improbable ni improbable probable

Se ha completado la entrevista. Muchas gracias

Sección III

SECCIÓN A. CARGA QUE SIGNIFICÓ EL ESTUDIO

Las siguientes preguntas se refieren a sus sentimientos respecto a su participación en el estudio. Por favor díganos el grado en el que está de acuerdo con las siguientes afirmaciones.

Sentí molestia debido a ...

1. La cantidad de visitas del estudio
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

2. El tiempo necesario para las visitas del estudio
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

3. Tener que viajar al centro de estudio
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

4. El tiempo necesario de espera en las visitas del estudio
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

5. Someterme a exámenes pélvicos
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

6. Someterme a una colposcopia (cuando el médico observó dentro de mi vagina con el instrumento de aumento)
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

7. No poder utilizar duchas vaginales durante el estudio
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

8. No poder utilizar lubricantes vaginales durante el estudio
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

9. Tener que aplicar diariamente el gel de estudio
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

10. Tener que utilizar el gel de estudio durante el sexo
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

11. Tener que utilizar condones durante el sexo mientras participé en el estudio
 1. Estoy totalmente en desacuerdo
 2. Estoy algo en desacuerdo
 3. Estoy algo de acuerdo
 4. Estoy totalmente de acuerdo

12. ¿Alguna vez tuvo problemas para entender las instrucciones escritas sobre la forma de utilizar el gel?
[0] No
[1] Sí

13. Opina que su compensación por participar en este estudio...
 1. No fue suficiente
 2. Estuvo bien
 3. Fue más de lo necesario

Se ha completado la entrevista. Muchas gracias

Section 14. Data Collection

The purpose of this document is to provide site staff with the information they need to successfully complete and submit MTN 004 case report forms. For questions about this section or about general data collection policies, procedures, or materials, please contact Missy Cianciola (see e-mail addresses listed below).

For this study, the SDMC (Statistical and Data Management Center) is SCHARP (the Statistical Center for HIV/AIDS Research and Prevention). SCHARP is located in Seattle, USA, and is in the US Pacific Time (PT) time zone. The SCHARP MTN 004 team members, along with their job role and e-mail addresses, are listed in Section 16 of this manual.

14.1 DataFax Overview

DataFax is the data management system used by SCHARP to receive and manage data collected at study sites. The site faxes an electronic image of each case report form (CRF) to SCHARP DataFax, and the original hard copy CRF is retained by the site.

CRF Transmission

Case report forms can be transmitted to SCHARP in one of two ways: faxed using a fax machine connected to a land phone line (fax to phone number 206.667.4805); or faxed using a fax machine connected to the internet (fax to e-mail <datafax@scharp.org>).

SCHARP's Information Systems Technology (IST) group is available to consult with the site to determine the best method for data transmission. The SCHARP IST group can be contacted via e-mail at support@scharp.org. The SCHARP IST group should also be contacted anytime the site has technical questions or problems with their fax equipment.

Data Entry/Quality Control

Once a CRF image is received by SCHARP DataFax, the following occurs:

- DataFax identifies the study to which each CRF belongs using the barcode at the top of the form. It reads and enters the data into the study database and stores each CRF on a computer disk.
- Next, each CRF is reviewed by at least two members of SCHARP's Data Operations Group. Problems such as missing or potentially incorrect data are identified and marked with Quality Control notes (QCs).
- QCs are compiled into QC reports that are sent via e-mail to the study site on a regular basis. Sites are asked to correct or clarify any problems identified on the QC reports and refax the corrected CRFs to SCHARP DataFax.
- When the re-faxed pages are received, SCHARP staff review the corrected pages and resolve the QCs

If a change is made to a CRF but the updated page is not re-faxed to SCHARP DataFax, the change will not be entered and the study database will continue to contain incomplete or incorrect data. Additionally, if the change was prompted by a QC, the QC will continue to appear on subsequent QC reports until the modified CRF is received at SCHARP. Therefore, it is very important that the site refax updated CRF pages to SCHARP DataFax **any time** a change is made to a CRF, regardless of whether or not the change was made in response to a QC report.

14.2 DataFax Form Completion

14.2.1 Guidelines

Based on the use of fax technology and Good Clinical Practices (GCPs), the following guidelines should be used for completing DataFax CRFs:

- Use a black or dark blue medium ballpoint pen. Do not use any other type of writing tool. Use only one color per form. That is, do not begin completing a form using a blue pen and then switch to a black pen during the same form completion session.
- Press firmly when recording data or writing comments.
- Print all data and comments legibly by hand. Entries that cannot be read will result in QC notes.
- Do not type data onto CRFs. Do not use cursive/script handwriting, as it can be difficult to read.
- Write numbers as large as possible while staying within the boundaries of the boxes.
- Record data on the front of CRFs only. DataFax cannot read the back of CRFs.
- Do not record data or make marks in the 0.5-inch/1.5-cm margins at the top, bottom, or sides of the CRF.
- If the lines provided for written responses are not long enough, continue in another blank area of the form (within the page margins).
- Mark only one answer except when given the instruction “Mark all that apply.”
- A response is required for every item unless instructed otherwise by a skip pattern.
- **Never** obscure, mark over, or punch holes through the barcode at the top of each CRF. DataFax requires the barcode to identify the CRF.
- **Never** use correction fluid (“white-out”) or correction tape on CRFs.
- Remove any paper clips, staples, or other attachments before faxing CRFs.
- The site staff person who initially completes the form **must** record his/her initials **and** the date in the space provided in the bottom right-hand corner of each CRF page.
- Fax forms as soon as possible after they have been completed and reviewed. Ideally, completed forms will be faxed to SCHARP within 1–2 days of completing the visit, though up to 5 days is allowed.

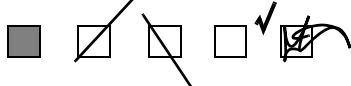
14.2.2 How to Mark Response Boxes

Many items on DataFax CRFs have a box or series of boxes for recording a response. Mark the box clearly with an **X**. Do not fill in the box with shading or mark it with a slash or other character.

Correct:



Incorrect:



Mark only one response box for each item unless the “Mark all that apply” instruction is present.

14.2.3 How to Record Numbers

Some questions on DataFax CRFs include boxes for recording a numeric response. DataFax can only read the numbers in these boxes if they are recorded clearly. The following instructions should be followed when recording numeric responses:

- Right justify **all** numbers and fill in any blank leading boxes with zeroes. If boxes are left blank, a QC note will be applied asking for the boxes to be filled in.

The following example shows how a value of 7 is recorded when three response boxes are provided:

Correct:

0 0 7

Incorrect:

□ □ 7

This example would result in a QC note.

- Write the number(s) as large as possible while staying within the boundaries of the box; try not to stray outside the boundaries of the box.

In the following example, the 4 could be misinterpreted as a 7 or a 1 because DataFax can only read what is *inside* the box:

Correct:

4

Incorrect:

4

- Write the number(s) simply, with few loops.

The following example shows the format in which numbers will be most easily read by DataFax. Also included are some commonly used formats that may be difficult for DataFax to identify.

Easily Identified:

0 1 2 3 4 5 6 7 8 9

Difficult to Identify:

ø 1 2 3 4 7

14.2.4 How to Record Dates

Dates are recorded using the “dd MMM yy” format, where “dd” represents the two-digit day, “MMM” represents the three-letter abbreviation of the month (in capital letters), and “yy” represents the last two digits of the year.

The month field must be filled in with the three-letter abbreviation *in English* for the date to be read in DataFax. Abbreviations are shown below:

Month	Abbreviation	Month	Abbreviation
January	JAN	July	JUL

Month	Abbreviation	Month	Abbreviation
February	FEB	August	AUG
March	MAR	September	SEP
April	APR	October	OCT
May	MAY	November	NOV
June	JUN	December	DEC

For example, June 6, 2008 is recorded as:

0	6	J	U	N	0	8
<i>dd</i>		<i>MMM</i>			<i>yy</i>	

Sometimes, only a month and a year are required (e.g., diagnosis date for a pre-existing condition), in which case the response boxes will look like this:

<i>MMM</i>			<i>yy</i>	

A diagnosis date of October, 2008 would be recorded as follows:

O	C	T	0	8
<i>MMM</i>			<i>yy</i>	

14.2.5 How to Record Time

Time is recorded on DataFax CRFs using the 24-hour clock (00:00-23:59), in which hours are designated from 0–23. For example, in the 24-hour clock 2:25 p.m. translates to 14:25 (2 p.m. = 14), which would be recorded as follows:

1	4	:	2	5
<i>hr</i>			<i>min</i>	

Midnight is recorded as 00:00, not 24:00.

The following chart shows equivalencies between the 12- and 24-hour clocks:

12-hour clock (a.m.)	24-hour clock	12-hour clock (p.m.)	24-hour clock
Midnight	00:00	Noon	12:00
1:00 a.m.	01:00	1:00 p.m.	13:00
2:00 a.m.	02:00	2:00 p.m.	14:00
3:00 a.m.	03:00	3:00 p.m.	15:00
4:00 a.m.	04:00	4:00 p.m.	16:00
5:00 a.m.	05:00	5:00 p.m.	17:00
6:00 a.m.	06:00	6:00 p.m.	18:00
7:00 a.m.	07:00	7:00 p.m.	19:00
8:00 a.m.	08:00	8:00 p.m.	20:00
9:00 a.m.	09:00	9:00 p.m.	21:00
10:00 a.m.	10:00	10:00 p.m.	22:00
11:00 a.m.	11:00	11:00 p.m.	23:00

14.2.6 Data Corrections and Additions

Sometimes, data on a DataFax CRF may need to be changed, clarified, or amended. There are many reasons why data may need to be changed, such as in response to a QC report or as a result of site review of the CRF before faxing.

It is important to make these changes to the original CRF—*never* copy data onto a new form. After making the change, the CRF *must* be re-faxed to SCHARP DataFax.

Note: If a correction or addition is made to one page of a multiple-page CRF, only refax the page that was changed.

Note: Never write over an entry once it is recorded. Use the standards outlined in the following paragraphs when changing, clarifying, or amending data.

Whenever an entry on a DataFax CRF is changed, do the following:

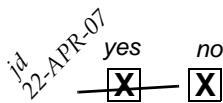
- draw a single horizontal line through the incorrect entry (do not obscure the entry or make it unreadable with multiple cross-outs)

- place the correct or clarified answer near the box, and initial and date the correction as shown below:



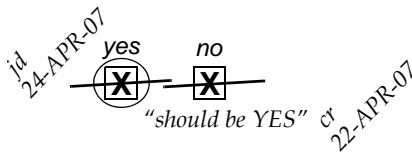
If an **X** is marked in the wrong response box, correct it by doing the following:

- draw a single horizontal line through the incorrectly marked box
- mark the correct box, and
- initial and date the correction as shown below:



If the correct answer has previously been crossed out, do the following:

- circle the correct item
- write an explanation in the white space near the item, and
- initial and date all corrections as shown below:

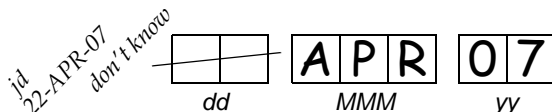


The standards above must **always** be followed whenever a CRF is changed, clarified, or amended, even if the change is made **before** the CRF is faxed to SCHARP for the first time.

14.2.7 How to Handle Missing and Unknown Data

If the answer to an item is not known, is not available, or if the participant refuses to answer, draw a single horizontal line through the blank boxes and initial and date the item. It is helpful to write “don’t know,” “refuses to answer,” “UNK” (unknown), “N/A” (not applicable), or “REF” (refused) near the blank boxes.

For example, when recording a date, if the exact day is not known, draw a single horizontal line through the “dd” boxes and write “don’t know” next to the response boxes, as shown below:



A skip pattern is the **only** valid reason to leave a response blank. Initials and date are required for any data item that is refused, missing, unknown, or not applicable, regardless of whether it is marked as such during the initial form completion, or as an update to the form.

14.3 MTN 004 Study-Specific Data Collection Information

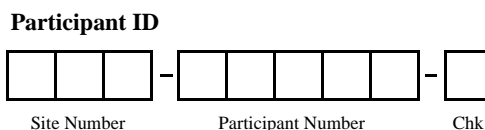
14.3.1 Participant ID numbers (PTIDs)

DataFax uses a unique participant identification number (PTID) to identify each study participant in the database. SCHARP provides each site with a list of PTIDs prior to study start-up. The site should assign one PTID to each participant enrolled in the study. The PTIDs are assigned in sequential order as participants screen for the study. The site should ensure that each PTID is assigned only once. Once a participant has received a PTID, she maintains that same PTID throughout the entire study.

PTID boxes are located near the upper left corner of each CRF page.

Site staff are responsible for maintaining a log linking PTIDs to participant names (PTID-Name Link log) in accordance with Section 3 of this manual.

The PTIDs used for this study are nine digits and formatted as “XXX-YYYYY-Z.” The PTID consists of three parts: the site number (XXX), the participant number (YYYYY), and a numerical check digit (Z). The check digit (Z) is a number generated by SCHARP with the participant number, and helps ensure that the correct PTID is recorded. Below is an example of the PTID structure used in MTN 004.



14.3.2 Study Visit Timing

Screening Attempt

Each time a participant screens (each time she provides written informed consent for screening), it is called a *screening attempt*. Because sites have 36 calendar days to complete screening and enrollment procedures, the visit dates/specimen collection dates on forms completed as part of the same screening attempt may be different from each other. The 36-day screening attempt “clock” starts on and includes the day the consent form for screening is signed or marked by the participant.

Multiple Screening Attempts (Re-screens)

If a participant’s screening attempt is unsuccessful, she may re-screen for the study if she chooses. If she does re-screen, ALL screening procedures (except PTID assignment), evaluations, and forms must be repeated, including signing of the written informed consent for screening.

Completion of Required Follow-Up Visits

Required follow-up visits are regularly scheduled every week throughout the three-week study follow-up period. Per protocol, study visits should be completed within the protocol-specified visit windows. However, there may be cases when a regularly scheduled visit is made up outside of the visit window. A regularly scheduled follow-up visit is considered “missed” when a participant does not complete any of the required visit evaluations, and the next visit window has opened. For example, a participant has a One-Week Clinic Visit target date of 17-APR-07 (visit window 16-APR-07 to 18-APR-07). Her Two-Week Clinic Visit window opens 23-APR-07, and the participant does not come into the clinic until 24-APR-07 for her scheduled Two-Week Clinic Visit. Since the participant did not complete the One-Week Clinic Visit within the visit window AND did not make up the missed One-Week Clinic Visit before the Two-

Week Clinic Visit window opened (23-APR-07), the One-Week Clinic Visit is considered “missed.” A Missed Visit form is completed and faxed to SCHARP to document the “missed” visit.

Interim Visits

A clinic visit is considered an Interim Visit when a participant presents at the site for additional clinical/laboratory/pharmacy assessments and/or procedures *outside* of the required evaluations for a scheduled study visit. The following are examples of interim visits for MTN 004:

1. A participant completes all required evaluations for a scheduled study visit within the visit window. She then returns to the site clinic within the same visit window to request replacement study gel cartons for lost study gel.
2. A participant completes all required evaluations for a scheduled study visit within the visit window. She then returns to the clinic outside the visit window to request a pregnancy test.
3. A participant completes all required evaluations for a scheduled study visit outside the visit window (the visit is made up late, after the visit window has closed). She then returns to the clinic 48-72 hours after the visit (still outside the visit window) for a repeat pelvic exam and clinical follow-up of superficial epithelial disruption (abrasion/peeling) noted during the visit pelvic exam.
4. A participant completes all required evaluations for a scheduled study visit outside the visit window (the visit is completed early, before the window has opened, due to participant travel during the visit window). She then returns to the clinic after the visit window has closed (and before the next visit window has opened) to report intermenstrual bleeding.

Phone contact with a participant is also considered an Interim Visit if the phone contact results in reporting of a new Adverse Experience (AE).

- Example: A participant’s One-Week target visit date is 17-APR-07. She completes all required evaluations for the visit on 16-APR-07. On 18-APR-07 she calls the clinic to report new symptoms, which result in the reporting of a new adverse experience. Although she is still within the visit window (16-APR-07 to 18-APR-07), she has already completed all the required One-Week Visit evaluations. Thus, the 18-APR-07 phone contact is assigned an Interim Visit code.
- Example: A participant’s Two-Week target visit date is 24-APR-07. She completes all required evaluations for the visit on 25-APR-07. On 28-APR-07 she calls the clinic to report new symptoms which result in the reporting of a new adverse experience. Since she already completed all the required visit evaluations, and since the Three-Week Visit window has not yet opened, the 28-APR-07 phone contact is assigned an Interim Visit code.

Note: Study visits conducted early, before a visit window opens (e.g., due to anticipated travel by the participant during the visit window), or made up late, after a visit window has closed, are not considered Interim Visits. Such visits should be coded using the scheduled study visit code (One-Week=03.0, Two-Week=04.0, etc.). All forms that document required evaluations for a given study visit should be coded using the scheduled study visit code, regardless of whether the visit takes place within the visit window or outside the visit window (early or late). For example, forms documenting all required One-Week Clinic Visit procedures should be coded “03.0,” regardless of whether the required procedures are conducted within or outside the visit window. Consequently, additional visits required to complete scheduled study visit procedures (e.g., because a participant must leave the site before all procedures can be performed) are not considered Interim Visits. Such “split” visits also should be coded using the same scheduled study visit code.

For questions about phone contacts and assignment of visit codes to such contacts, please contact the SCHARP MTN 004 Project Manager.

14.3.3 Visit Codes and Page Numbers

Some DataFax CRFs will include boxes in the upper right corner for a visit code. DataFax uses the visit code to identify the visit at which a CRF is completed. However, not all DataFax CRFs include boxes for visit codes. If a form is only completed once during a study (for example, the Enrollment form, the Termination form), the visit code will be automatically assigned in DataFax.

MTN 004 has six scheduled study visits. When visit code boxes are provided, site staff are responsible for entering the visit code in the boxes provided in the upper right corner of each page.

The following table lists visit type, timing, and DataFax visit codes for each visit.

Table 14-1: Visit Timing and Visit Codes

Visit Type	Timing	Visit Code
Screening 1	Up to Day -36	01.0
Screening 2	Up to Day -36	01.0
Enrollment	Day 0	02.0
One-Week Visit	Day 6-8	03.0
Two-Week Visit	Day 13-15	04.0
Three-Week Visit	Day 20-24	05.0

Visit Codes for visits that occur over more than one calendar day

In cases when a participant absolutely cannot complete all required visit evaluations in one day (for example, she is menstruating and a pelvic/colposcopy exam cannot be performed), complete as many of the required evaluations as possible. Schedule the participant for another visit to conduct the remaining required evaluations as soon as possible, and preferably within the visit window. Note that when the participant returns to complete the remaining required evaluations, these are still considered part of her regular visit (regardless of whether or not they occur within visit window); therefore, the forms completed for these remaining evaluations should be assigned the same regular visit code as the previous visit.

- Example: A participant's Two-Week Clinic Visit target date is 24-APR-07 (visit window is 23-APR-07 to 25-APR-07). The participant comes to the clinic on 23-APR-07 for her Two-Week Clinic Visit and is on her menses. On 23-APR-07 (Visit Code = 04.0), complete all study visit evaluations except the pelvic exam and pelvic laboratory assays. Instruct the participant to come back to the clinic on 26-APR-07 (when menses is expected to have ended) to complete the required pelvic exam and pelvic laboratory assays. The forms completed at the 26-APR-07 visit are assigned the same Two-Week Visit Code as the 23-APR-07 forms (Visit Code = 04.0), since the required evaluations for the Two-Week Clinic Visit were conducted on both dates.

Visit codes for interim visits

In addition to the scheduled, protocol-required visits listed in Table 14-1, interim visits may occur once the participant is enrolled (see Section 14.3.2 for a definition and examples of interim visits). Interim visit codes are assigned using the following guidelines:

- In the boxes to the left of the decimal point, record the two-digit visit code for the most recent scheduled visit (whether that visit was completed or missed).
- Use the guide below to complete the box to the right of the decimal point:
 - ##.1 = the first interim visit after the most recent scheduled visit,
 - ##.2 = the second interim visit after the most recent scheduled visit,
 - ##.3 = the third interim visit after the most recent scheduled visit, and so on.

Example #1: A participant returns to the site clinic two days after she has completed her One-Week Clinic Visit (Visit Code = 03.0). The visit window of her Two-Week Clinic Visit has not yet opened. For this interim visit, record the following visit code:

Visit Code for this Interim Visit:

Visit Code .

Example #2: A participant returns to the site clinic again two days after her 03.1 interim visit (described in Example #1). The visit window for her Two-Week Clinic Visit has not yet opened. Record the following visit code:

Visit Code for this Interim Visit:

Visit Code .

Page numbers

Other CRFs, such as log forms (e.g., Adverse Experience Log or Concomitant Medications Log), may include boxes in the upper right corner for page numbers, as shown below:

Page

In the example of the Adverse Experience Log, the participant's first adverse experience would be reported as page 01, the second would be 02, and so on.

14.3.4 Staff Initials/Date

Most forms include a line in the lower-right corner for a staff member's initials and the date on which the form was completed. When more than one staff member records data on a CRF, the site should designate the staff member who has primary responsibility for the form. This individual completes the staff initials/date field. The individual not identified in the staff initials/date field writes his/her initials and date next to each data element for which he/she is responsible.

14.3.5 Case Report Form Completion Schedule

The SCHARP-provided case report forms for this study include DataFax forms (forms that are completed and faxed to SCHARP DataFax) and non-DataFax forms (forms that are completed but **not** faxed to SCHARP DataFax).

Some SCHARP-provided forms are required to be completed at each visit, while other forms are required only at one visit or only when specifically indicated. The following table (Table 14-3) lists the DataFax and non-DataFax forms that are **required** to be completed at each study visit.

Table 14-2: MTN 004 Case Report Form Completion Schedule

Visit	Visit Code	Forms	Form Acronym
Screening 1	1.0	Screening Consent Demographics Screening 1 and Enrollment Pelvic Exam Pelvic Laboratory Results Safety Laboratory Results STI Laboratory Results Concomitant Medications Log (non-DataFax) Baseline Medical History (non-DataFax) History of Genital Symptoms (non-DataFax) Physical Exam (non-DataFax) Pelvic Exam Diagrams (non-DataFax) Screening 1 Visit Eligibility (non-DataFax) Clinical Eligibility (non-DataFax) Screening Summary (non-DataFax) LDMS Specimen Tracking Sheet	SC-1 DEM-1 SPE-1 thru SPE-2 PLR-1 SL-1 thru SL-2 SLR-1 thru SLR-2 CM-1 N/A 2 pages N/A N/A N/A N/A 4 pages N/A N/A 2 pages N/A
Screening 2	1.0	(non-DataFax) Screening 2 Visit/Enrollment Eligibility	N/A 2 pages
Enrollment	2.0	Family Planning Methods Baseline Genital Symptoms Screening 1 and Enrollment Pelvic Exam Pelvic Laboratory Results Safety Laboratory Results Pre-existing Conditions Enrollment Pharmacokinetics (non-DataFax) Physical Exam (non-DataFax) Pelvic Exam Diagrams (non-DataFax) Clinical Eligibility (non-DataFax) LDMS Specimen Tracking Sheet	FPM-1 BGS-1 SPE-1 thru SPE-2 PLR-1 SL-1 thru SL-2 PRE-1 ENR-1 PK-1 N/A N/A N/A N/A

Table 14-2: MTN 004 Case Report Form Completion Schedule

Visit	Visit Code	Forms	Form Acronym
One-Week Clinic Visit	3.0	Follow-Up Visit Family Planning Methods StudyGel Adherence Follow-up Genital Symptoms Follow-up Pelvic Exam Pelvic Laboratory Results Safety Laboratory Results (non-DataFax) Follow-Up Medical History (non-DataFax) Physical Exam (non-DataFax) Pelvic Exam Diagrams (non-DataFax) LDMS Specimen Tracking Sheet	FV-1 FPM-1 SGA-1 FGS-1 FPE-1 thru FPE-3 PLR-1 SL-1 thru SL-2 N/A 2 pages N/A N/A N/A
Two-Week Clinic Visit	4.0	Follow-Up Visit Family Planning Methods Study Gel Adherence Acceptability Assessment Follow-up Genital Symptoms Follow-up Pelvic Exam Pelvic Laboratory Results Safety Laboratory Results Pharmacokinetics (non-DataFax) Follow-up Medical History (non-DataFax) Physical Exam (non-DataFax) Pelvic Exam Diagrams (non-DataFax) LDMS Specimen Tracking Sheet	FV-1 FPM-1 SGA-1 AA-1 thru AA-2 FGS-1 FPE-1 thru FPE-3 PLR-1 SL-1 thru SL-2 PK-1 N/A 2 pages N/A N/A N/A
Three-Week Clinic Visit	5.0	Follow-Up Visit Family Planning Methods Follow-up Genital Symptoms Follow-up Pelvic Exam Pelvic Laboratory Results CASI Tracking Termination End of Study Inventory (non-DataFax) Follow-up Medical History (non-DataFax) Physical Exam (non-DataFax) Pelvic Exam Diagrams (non-DataFax) LDMS Specimen Tracking Sheet	FV-1 FPM-1 FGS-1 FPE-1 thru FPE-3 PLR-1 CT-1 TM-1 ESI-1 N/A 2 pages N/A N/A N/A

Table 14-2: MTN 004 Case Report Form Completion Schedule

Visit	Visit Code	Forms	Form Acronym
If Indicated	Will Vary	Follow-up Pelvic Exam Pelvic Laboratory Results Safety Laboratory Results STI Laboratory Results HSV-2 Culture Adverse Experience Log Interim Visit Product Hold/Discontinuation Genital Bleeding Assessment HIV Test Results Pregnancy Report and History Pregnancy Outcome Missed Visit (non-DataFax) Physical Exam (non-DataFax) Pelvic Exam Diagrams (non-DataFax) Specimen Tracking Sheet	FPE-1 thru FPE-3 PLR-1 SL-1 thru SL-2 SLR-1 thru SLR-2 HSR-1 AE-1 IV-1 PH-1 GBA 1-3 HTR-1 PR-1 PO-1 MV-1 N/A N/A N/A

14.3.6 Site Review of DataFax Forms

Each form must be reviewed for completeness and legibility before being faxed to SCHARP DataFax. As part of the review, the site should check the following:

- Other than the participant ID number (PTID), there is no information on the form that could identify the participant (e.g., name, phone number, national identification number, or any other personal identifiers).
- A response has been recorded for each item, unless the item was skipped as instructed by a skip pattern or the item was marked as missing or unknown as described in 14.2.7.
- All text responses are clearly recorded.
- There are no marks on or above the DataFax barcode at the top of each DataFax page.
- There are no:
 - missing dates,
 - missing visit codes,
 - incorrect PTIDs,
 - incorrect visit codes,
 - missing data for items beginning a series of skip patterns, and/or
 - inconsistent or discrepant data.

While CRFs are being reviewed, it is important that they are stored and tracked systematically. It is also necessary to have a system to identify whether a CRF has been faxed to SCHARP DataFax. Such a system may include using a stamp to date the back of the CRF, or utilizing the SCHARP CRF Tracking System (see SSP Section 14.3.7 for more information).

Important: If a date stamp is used to document when the form is faxed, stamp *only* the back of the CRF, *never* the front. Be sure to date stamp the back of the CRF each time it is faxed, including refaxes.

14.3.7 Faxing DataFax Forms

To streamline the submission of DataFax forms, the site should identify which staff members will be responsible for faxing forms to SCHARP DataFax and receiving and responding to QC reports.

It is important that the sites fax completed DataFax CRFs to SCHARP within the time period specified in the site's MTN 004 Data Management SOP, and that they respond promptly to requests for clarifications and corrections included in QC reports. Early detection of recurrent problems provides an opportunity to reduce errors and improve data quality.

For sites wishing to confirm the receipt of faxed forms at SCHARP, the CRF Tracking System (CTS) is available. This system generates two types of e-mails listings: 1) the number of form pages received at SCHARP; and 2) which specific forms were received at SCHARP for a given PTID and visit. Please contact the MTN 004 Project Manager if you would like to use the CRF Tracking System or for more information about the CRF Tracking System.

14.3.8 Non-DataFax Forms

MTN 004 sites will receive non-DataFax forms from SCHARP. These forms will be easily identifiable because there will not be a DataFax barcode along the top of the CRF. In place of the barcode, the following text will appear: "NOT A DATAFAX FORM. DO NOT FAX TO DATAFAX."

These forms should **not** be faxed to SCHARP DataFax. Instead, they should be kept in the participant's file as a record of the activities recorded on the form. The form completion guidelines described in sections 14.3.1 through 14.3.4 should be applied when completing non-DataFax CRFs as well.

14.4 Form Supply and Storage

14.4.1 Form and Specimen Label Supply

All case report forms needed for the study will be provided by SCHARP. Forms will be supplied using form visit packets, where the packet contains all of the required CRFs for the visit. For example, the Screening Visit packet will include all of the CRFs listed for this visit in the Case Report Form Completion Schedule table (table 13-3). In addition for form packets for each visit listed in Table 13-3, bulk supplies of "as needed" CRFs will be provided to the site (for example, Pregnancy Report and History, Pregnancy Outcome, Genital Bleeding Assessment, etc.).

SCHARP will also ensure sites have access to specimen labels (either printed on-site or printed by SCHARP). Specimen labels should be used for all primary specimen collection containers. Customized PK labels for use on PK specimen primary collection containers will also be provided. Please refer to the Laboratory section of the manual for more information on laboratory specimen collection and labeling.

14.4.2 Form Storage

Specifications for form storage will be detailed in the site's MTN 001 Data Management SOP. It is recommended that for each participant, study CRFs be stored in a hard-cover notebook. SCHARP can provide a template for use in creating notebook cover labels and spine labels. SCHARP can also provide a template that can be used to create tab dividers.

It is suggested that Concomitant Medications Log forms, Adverse Experience Log forms, and Product Hold/Discontinuation forms be kept in their own tabbed sections within the participant study notebook. This makes page numbering and updating of these forms easier than if these forms are stored by visit within the participant's study notebook.

14.5 How to Complete Interviewer-administered Forms

In order to standardize interviewer-administered data collection from site to site and to maximize quality, it is critical that participant interviews be conducted with a non-biased, non-judgmental approach. Study staff should help a participant feel comfortable sharing personal information and opinions while asking the study questions in a consistent manner from participant to participant.

Interviewing Techniques

An interviewer uses both verbal and non-verbal techniques to obtain the most honest, accurate, and thorough responses from participants. These techniques are discussed in the sections below.

Welcoming the Participant

- When a new participant arrives at the clinic, everything about the study is new. Help make the participant feel comfortable.
- Perhaps offer the participant a glass of water or other beverage.
- Introduce yourself, and try to create rapport (connection) between yourself and the participant to help her feel comfortable during the interview.
- Some DataFax forms include introduction statements before certain items to help prepare the participant for sensitive questions. Read each of these introductions as they appear on the forms.

Asking Sensitive Questions

This study is about a very sensitive subject: HIV. Gaining an understanding of sexual behavior patterns can affect the transmission of HIV and the development of prevention methods.

Your level of comfort with asking sensitive questions will affect the participant's comfort and answers. If you ask the questions in a confident and supportive manner, the participant will feel more confident and comfortable answering the questions. Make eye contact with the participant to let her know that you are listening to her and aware that she is being asked difficult questions. Avoid apologizing for questions or making facial gestures that might show you feel any way but neutral about a question or the participant's response. If the participant feels judged for her behavior, she will be less likely to share honestly with you.

Recording Participants' Responses Verbatim

Often, interviewer-administered questions will have a list of response categories provided to capture the participant's response. Almost always, an "other, specify" box is included as one of the response categories in order to capture participant responses that do not fit into one of the categories already listed. When a

participant's response does not match or fit into one of the listed response categories, record the participant's verbatim (word-for-word) response on the line labeled "Local Language" (even if the participant's response is in English). Record the participant's response in the language spoken by the participant. Once the interview is over, go back and translate the text recorded on the "Local Language" line into English, and record the English translation of the response on the "English" line. If the participant's response was in English originally, leave the "English" line blank.

Pacing the Interview

Every participant is different. Some will know or say the answer to questions very quickly. Others may have to think longer to come up with answers, or may change their answers after giving more thought to the subject. Always account for this variety when doing an interview. Read items slowly. Let the participant finish thinking before you record her response and go on to the next item.

Reading Items Aloud

Read all items to the participant **word-for-word**, and speak clearly. Avoid re-phrasing items because this can change the meaning of the item, making it inconsistent with another participant's interview. Provide explanation or interpretation if necessary only after reading the item word-for-word. Avoid tangential—though related—counseling and educational discussions during data collection. When applicable, acknowledge questions and concerns raised by the participant during the interview, and state that the subject can be discussed after the end of the interview.

Vary your tone of voice, so that you don't sound automated. Emphasize the important words in an item, so that the meaning of the question comes through.

When given the option, choose "clinical" versus "street" or "vernacular" language based on participant preferences/cues.

For items with multiple sub-items, read all sub-items to the participant and mark the appropriate response for each, based on participant report.

Probing

One of the major goals of the study's interviews is to obtain accurate information on many HIV related behaviors. These interviews ask participants to recall many aspects of personal behaviors. However, participants may not remember or know the answer to every question. The technique for helping a participant remember an answer, clarify a response, decide between two similar but different answers, or report something more precisely is called "probing."

Effective probing helps a participant think more about a question or refine an answer that is too general, however, probing must not bias or otherwise direct participant responses. As the interviewer, you cannot offer the participant an answer. Therefore, all probes must be neutral.

The following are some probing strategies to use when a participant initially answers "don't know" to an item or cannot refine her response enough for the item to be adequately recorded.

- **Repeat Probe:** The repeat probe is used by repeating the item or response categories (if the response categories are part of the question). Although the participant might hear you the first time you ask a question, she may need to hear the question more than once to provide an answer. Instead of rephrasing a question if you notice the participant is confused, always first repeat the item as it is written. Sometimes hearing the question a second time is all that is needed.
- **Echo Probe:** The echo probe involves repeating the participant's exact response. Sometimes hearing the answer with a different voice will help her be more precise. The echo should always be repeated in a neutral, non-judgmental style.

- **Silent Probe:** The silent probe is used by pausing briefly after a participant gives what seems to be an uncertain answer. Although silence can feel awkward, sometimes it is helpful when a participant is trying to determine the most accurate answer to a question. Use a silent probe when the participant sounds unsure of her answer and may need some extra time to think more carefully about the question.
- **Non-verbal Probe:** The non-verbal probe is used by giving hand or facial gestures that may help the participant to come up with an answer. Remember that all such gestures must be neutral and non-judgemental.
- **Specification Probe:** The specification probe is used by asking the participant to give a more precise answer. Although a participant may give an answer that he or she considers accurate, it may not be specific enough. For example, if an item asks how many times the participant did something and she answers with a range (“5 to 10”). Ranges are not acceptable for this type of interviewing. In this case, the probe, “Can you be more specific?” is often enough to help the participant choose the most accurate response.
- **Historical Probe:** The historical probe is used by asking whether the event in question occurred anytime around major holidays or personal events such as a birthday or other life event. Some items require the participant to recall dates, and initially she may be unable to recall a date. Referencing a calendar can also help the participant remember dates.

Watching for Non-verbal Cues

A participant may give you one answer verbally, but express something else using body language or facial expressions. Although you should not question a participant so as to make her feel like you don't trust her answers, be aware of whether she is giving you non-verbal cues that indicate she is not feeling comfortable, not taking the interview seriously, or not answering honestly.

Checking Your Work

During the interview it is important to use the forms instructions (those on the front and back of each page) to guide the interview. Also, make sure the participant is understanding and responding to you, and record all reported information on the forms. **After the interview and while the participant is still there**, review the forms for accuracy and completeness so you can complete an item that might have accidentally been missed. **Once the participant has left, any items identified as missed must remain as is and will be considered “missing data”**. Because all interviewer-administered CRFs are source documents (with the participant being the source of the data), missing items cannot be completed once the participant has left the clinic. For items identified as “missed”, please line through the item and write “item missed in error” in the white space next to the item, and initial and date.

14.6 Form Completion Instructions

Detailed form completion instructions for each form are provided on the back of each form page. These instructions include the purpose of each form as well as how each form should be completed. Some items on forms are straightforward and do not require specific instructions. Therefore, you will not see all form items listed in the form-specific completion instructions, but rather, only those items needing detailed explanation.

Below are some additional instructions for the **Pre-existing Conditions**, **Concomitant Medications Log**, and **Adverse Experience Log** case report forms.

Pre-existing Conditions and Concomitant Medication Log

- For the Pre-existing Conditions and Concomitant Medication Log forms, note that you should fax each page to SCHARP any time a new entry is added or modified, even if the page is not complete. You should **not** wait to complete all entries on a page before faxing to SCHARP.

Adverse Experience Log (AE Log)

- For the Adverse Experience Log form, do **not** wait until the AE resolves before faxing the form page to SCHARP. In most cases, when you first report the AE on an AE Log form, the AE will have a “continuing” status (form item 6). Once the AE resolves (the AE resolves, the AE is grade 5 - death, or the AE increases in severity/frequency), update item 6 and 6a of the **original** AE Log form page. Initial and date all additions, and refax the form page to SCHARP.
- Always make changes, corrections, and updates to the **originally-completed** Adverse Experience Log form page. Once an AE Log form page has been started and faxed to SCHARP, the data from that page should **never** be transcribed onto another AE Log form page. All updates and corrections should be made to the originally-completed form page (regardless of how messy or crowded the form page becomes).
- For item 1, note that planned procedures or surgeries are **not** AEs. For example, a tonsillectomy is not an AE, and should not be reported as an AE. Any adverse experiences associated with the planned procedure or surgery are AEs and should be reported on an AE Log form. For example, a throat infection that resulted from the tonsillectomy is a reportable AE.
- Note that for **item 3**, the Female Genital Grading Table for Use in Microbicide Studies (Female Genital Tox Table) will be used to assign severity grades to AEs (in addition to the DAIDS “Tox Table”). The Female Genital Tox Table is Appendix V of the protocol. For **item 4**, note that if “not related” is marked, you need to record the reason the AE is determined to be “not related” in the Comments field of the form. For example, for an AE of headache that is judged “not related”, the Comments entry may be something like “#4 - not related in time to this AE onset”.
- For **item 5**, mark “no change” if the AE does not result in a product hold or discontinuation.
- For **item 7**, note that if the AE results in a new or prolonged hospitalization, the AE meets the criteria for “serious” and item 8 of the AE Log form should be marked “yes”.
- There may be a situation where an AE reported on an Adverse Experience Log form needs to be deleted (in the case where the AE is later found to actually be a pre-existing condition, for example). To indicate an AE Log page should be deleted, draw a diagonal line across the entire form page, write “delete due to _____” (include the reason the AE is being deleted), and initial and date. Refax the form to SCHARP. Do **not** reassign the page number assigned to the deleted AE to another AE, and do not renumber the other AE Log pages present for the participant.
- For **item 10**, note that the Visit Code recorded is the same visit code assigned to the visit date in the “Date Reported to Site” field.

14.7 Case Report Forms

This section contains each MTN 004 case report form developed for the study. Detailed form completion instructions for each form are provided on the back of each form page.

Use the Visit Checklist developed for the visit for a suggested order in which the forms should be completed at each visit.

CRF Table of Contents

Screening Consent	14-20	Family Planning Methods	14-74
Demographics.....	14-22	Baseline Genital Symptoms	14-76
Screening 1 and		Pre-existing Conditions	14-78
Enrollment Pelvic Exam	14-24	Enrollment	14-80
Pelvic Laboratory Results	14-28	Pharmacokinetics	14-82
Safety Laboratory Results	14-30	Follow-up Visit	14-84
STI Laboratory Results	14-34	Study Gel Adherence	14-86
Concomitant Medications Log	14-38	Follow-up Genital Symptoms	14-88
Baseline Medical		Follow-up Pelvic Exam	14-90
History (non-DataFax)	14-40	Follow-up Medical	
History of Genital		History (non-DataFax)	14-96
Symptoms (non-DataFax).....	14-44	Adverse Experience Log	14-100
Physical Exam (non-DataFax)	14-46	Product Hold/Discontinuation	14-102
Screening 1 Visit		Genital Bleeding Assessment	14-104
Eligibility (non-DataFax).....	14-48	Pregnancy Report and History	14-110
Clinical Eligibility (non-DataFax)	14-56	Pregnancy Outcome.....	14-112
Screening Summary (non-DataFax)	14-58	Missed Visit	14-114
Screening 2 Visit/Enrollment		Acceptability Assessment.....	14-116
Eligibility (non-DataFax).....	14-62	Interim Visit.....	14-120
HSV-2 Culture	14-66	CASI Tracking	14-122
LDMS Specimen Tracking		End of Study Inventory	14-124
Sheet (non-DataFax).....	14-68	Termination.....	14-126
HIV Test Results	14-70		
Pelvic Exam			
Diagrams (non-DataFax)	14-72		

SAMPLE. DO NOT FAX
TO DATAFAX

MTN 004 (136)



SC-1 (005)

Participant ID

			-							-	
Site Number				Participant Number							Chk

Screening Consent

Visit Date

dd		MMM				yy	

1. Is the participant between the ages of 18 and 24 years old? *yes* *no* → **If no, participant is ineligible. End of form.**

2. Was the participant able and willing to provide written informed consent for screening per local regulations and guidelines? *yes* *no* → **If no, participant is ineligible. End of form.**

2a. When was the informed consent form for screening marked or signed?

dd *MMM* *yy*

Comments: _____

Screening Consent (SC-1)

This form is used to document that a participant provided written informed consent for screening for this study. This form must be completed for each participant who is assigned an MTN 004 PTID.

This form is faxed to SCHARP DataFax only if the participant enrolls in the study, and only after completion of her Enrollment visit.

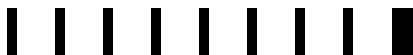
***Note:** If a participant is being re-screened, a new Screening Consent form must be completed as part of the subsequent screening attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

Item-specific Instructions:

***Note:** There is no visit code field on this form since this form is only administered during screening.*

- **Item 1:** According to the protocol, a participant must “be between the ages of 18 and 24 years-old at screening and enrollment, inclusive, and verified per site standard operating procedures (SOPs).” Participants who are under 18 years or over 24 years of age should not be screened for the study. If a participant reports that she is 24 years of age at screening, her Enrollment Visit must be conducted prior to her next birthday for her to be eligible to enroll per protocol.
- **Comments:** Record any necessary or additional information at the bottom of the form.

SAMPLE. Do NOT FAX
TO DATAFAX



MTN 004 (136)

DEM-1 (001)

Participant ID

- -

Site Number Participant Number Chk

Demographics

Form Completion Date

dd MMM yy

I will start by asking you some general questions about yourself.

1. What is your date of birth? → If unknown, record age:

dd MMM yy years

2. What is your gender? male female

NOT APPLICABLE FOR THIS PROTOCOL.

3. Do you consider yourself to be Latina or of Hispanic origin? yes no

4. What is your race? Read categories aloud. Mark all that apply.

- 4a. American Indian or Alaskan Native
- 4b. Asian
- 4c. Black or African American
- 4d. Native Hawaiian or Other Pacific Islander
- 4e. White
- 4f. Mixed
- 4g. other, specify:

Demographics (DEM-1)

This interviewer-administered form is used to collect participants' demographic and socioeconomic information.

This form is faxed to SCHARP DataFax only if the participant enrolls in the study, and only after completion of her Enrollment visit.

***Note:** If a participant is being re-screened, a new Demographics form must be completed as part of the subsequent screening attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

If the participant refuses to give a response to any item(s), draw a line through the response boxes, write "refused," and initial and date the note in the white space next to the item.

If the participant is unable to give a response to any item(s), mark the "don't know" box (if provided). Otherwise, draw a line through the response boxes, write "don't know," and initial and date the note in the white space next to the item.

General Interviewer Tips:

See Section 14.5 of the Study-Specific Procedures Manual for detailed interviewing techniques.

- Help the participant feel comfortable. Develop a rapport or connection with the participant.
- Avoid re-phrasing items, as doing so can change the meaning of the items and make them inconsistent with other interviews.
- Use probes to help the participant remember an answer, clarify a response, or to help report something more accurately.

It is important for you to review the forms for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

Item-specific Instructions:

***Note:** There is no visit code field on this form since this form is only administered during screening.*

- **Item 1:** If any portion of the date of birth is unknown, record age at time of enrollment. If age is unknown, record the participant's best estimate of her age. Do not complete both answers. *NOTE: participant must be between the ages of 18 and 24 years at the time of screening and enrollment, inclusive, and verified per site SOP, to be eligible for study participation.*
- **Item 4:** This item must be self-identified by the participant. This item asks about race. Read each category aloud and mark the response(s) that apply based on the participant's response. If the participant feels that an appropriate choice is not listed mark the "other, specify" box and record her response on the line provided.

SAMPLE Do NOT FAX TO DATAFAX

Visit Code

0

1

MTN 004 (136)

SPE-1 (041)

Participant ID

Site Number Participant Number Chk

Exam Date

dd MMM yy

Screening 1 and Enrollment Pelvic Exam

1. Naked eye, speculum, and bimanual exam assessments:

If no abnormal findings, go to item 2.

no abnormal findings

abnormal findings

If abnormal findings are noted, consult protocol to determine participant eligibility.

1a. Abnormal non-colposcopic findings: Mark all that apply.

- 1a1. enlarged/tender inguinal lymph nodes
1a2. abnormal vaginal discharge
1a3. abnormal cervical discharge
1a4. blood-tinged discharge
1a5. blood in vagina—no identified source
1a6. blood from cervical os
1a7. bleeding from site of epithelial disruption
1a8. erythema
1a9. ulceration
1a10. laceration
1a11. abrasion
1a12. peeling
1a13. petechia
1a14. ecchymosis
1a15. vesicles
1a16. edema
1a17. abnormal cysts
1a18. grossly white finding
1a19. mass
1a20. warts—on and/or interior to labia minora
1a21. warts—exterior to labia minora
1a22. adnexal tenderness
1a23. cervical motion tenderness
1a24. uterine tenderness
1a25. other abnormal findings, specify:

If finding is present at Enrollment, record on Pre-existing Conditions form.

2. Colposcopic exam assessment: Required at Enrollment Visit.

not done

no abnormal findings

abnormal findings

If not done OR no abnormal findings, go to item 3 on page 2.

If abnormal findings are noted, consult protocol to determine participant eligibility.

2a. Abnormal colposcopic findings: Mark all that apply.

- 2a1. abnormal vaginal discharge
2a2. abnormal cervical discharge
2a3. blood-tinged discharge
2a4. blood in vagina—no identified source
2a5. blood from cervical os
2a6. bleeding from site of epithelial disruption
2a7. erythema
2a8. ulceration
2a9. laceration
2a10. abrasion
2a11. peeling
2a12. petechia
2a13. ecchymosis
2a14. vesicles
2a15. edema
2a16. abnormal cysts
2a17. grossly white finding
2a18. mass
2a19. warts—on and/or interior to labia minora
2a20. warts—exterior to labia minora
2a21. other abnormal findings, specify:

If finding is present at Enrollment, record on Pre-existing Conditions form.

26-MAR-07

01

14-24

Language

Staff Initials / Date

Screening 1 and Enrollment Pelvic Exam (SPE-1)

This form, along with the non-DataFax Pelvic Exam Diagrams, is used to document the pelvic (and, when applicable, colposcopy) exams conducted during the Screening 1 and Enrollment Visits. This form should be completed once to document the Screening 1 Pelvic Exam, and once to document the Enrollment pelvic/colposcopy exam.

This form is faxed to SCHARP DataFax only if the participant enrolls in the study, and only after completion of her Enrollment Visit.

Note: *If a participant screens more than once for the study (i.e., has multiple screening attempts), and eventually enrolls in the study, only the Screening 1 and Enrollment Pelvic Exam form from the successful screening attempt that led to enrollment should be faxed to SCHARP. For each enrolled participant, only one Screening 1 and Enrollment Pelvic Exam form for the Screening 1 Visit (assigned visit code 1.0), and one Screening 1 and Enrollment Pelvic Exam form for the Enrollment Visit (assigned visit code 2.0) should be faxed to SCHARP DataFax.*

Item-specific Instructions:

- **Item 1:** Document only those abnormal findings observed during naked eye, speculum, and bimanual examinations. If no abnormal findings are observed, mark the “no abnormal findings” box, leave item 1a blank and go to item 2. If one or more abnormal findings are observed, mark the “abnormal findings” box and continue to item 1a.
- **Item 1a:** Mark the box to the left of **each** abnormal finding observed via naked eye, speculum, and bimanual examination **only**. If an observed abnormal finding is not listed, mark the “other abnormal findings, specify” box and describe the abnormal finding in the space provided.
- **Item 2:** Colposcopy is required at the Enrollment Visit. Document any abnormal findings observed during colposcopic examination **only**. If the exam did not include colposcopy, mark the “not done” box, leave item 2a blank and go to item 3. If colposcopy was required but not done, also record the reason it was not done in the Comments section at the bottom of page 2. If no abnormal findings are observed on colposcopy, mark the “no abnormal findings” box, leave item 2a blank and go to item 3. If one or more abnormal findings are observed, mark the “abnormal findings” box and continue to item 2a.
- **Item 2a:** Mark the box to the left of **each** abnormal finding observed on colposcopy **only**. If an observed abnormal finding is not listed, mark the “other abnormal findings, specify” box and describe the abnormal finding in the space provided.

SAMPLE. Do NOT FAX
TO DATAFAX

MTN 004 (136)



SPE-2 (042)

Visit Code . 0

1

Participant ID

- -
Site Number Participant Number Chk

Screening 1 and Enrollment Pelvic Exam

3. Do any of these exam findings involve deep epithelial disruption? yes no
If yes, participant is ineligible at this time. Complete remainder of form. **If no, go to item 4.**

3a. Was the deep epithelial disruption observed in more than one distinct area? yes no

4. Cervical Ectopy: Percentage of cervical surface area.
0% 1-25% 26-50% 51-75% > 75%

4a. Cervical ectopy assessed by: naked eye colposcopy

Alternate Collection Date

dd	MMM	yy		not required	stored	not stored	Reason:
<input type="text"/>	<input type="text"/>	<input type="text"/>	5. Gram stain (vaginal)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
<input type="text"/>	<input type="text"/>	<input type="text"/>	6. Cervical swabs.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
<input type="text"/>	<input type="text"/>	<input type="text"/>	7. Vaginal swab	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____

Comments: _____

Screening 1 and Enrollment Pelvic Exam (SPE-2)

- **Items 4 and 4a:** When colposcopy is performed, cervical ectopy must be assessed by colposcopy and not by naked eye. If colposcopy was performed, item 4a should be marked “colposcopy.” If colposcopy was not performed, item 4a should be marked “naked eye.”
- **Items 5–7:** Record the alternate collection date when the specimen(s) was *collected* for this visit if the date is not the same as the Exam Date (NOT the date results were reported or recorded on the form). Complete date required.
- **Item 5:** Collection of a vaginal Gram Stain smear (duplicate slides) is required as part of the Screening 1 and Enrollment Visit pelvic exams. If a vaginal Gram Stain smear was not collected, mark the “not stored” box and record the reason.
- **Item 6:** Collection of cervical swabs for cytokine and innate factor testing is required as part of the Enrollment Visit pelvic exam. If cervical swabs were not collected at the Enrollment Visit, mark the “not stored” box and record the reason. If this is the Screening 1 Visit pelvic exam, mark the “not required” box.
- **Item 7:** Collection of a vaginal swab for quantitative culture is required as part of the Enrollment Visit pelvic exam. If a vaginal swab was not collected at the Enrollment Visit, mark the “not stored” box and record the reason. If this is the Screening 1 Visit pelvic exam, mark the “not required” box.
- **Comments:** Record any necessary or additional information at the bottom of the form.

SAMPLE. Do NOT FAX
TO DATAFAX

Visit Code

□□□.□□

1

MTN 004 (136)

PLR-1 (143)

Participant ID

□□□-□□□□□□-□
Site Number Participant Number Chk

Pelvic Laboratory Results

Initial Specimen Collection Date
□□ □□□□ □□
dd MMM yy

Alternate Collection Date

Not done/ Not collected dd MMM yy
□ □□□ □□□□ □□□□
Not done

1. VAGINAL WET PREP STUDIES

- 1a. Homogeneous vaginal discharge *negative* *positive*
- 1b. pH..... □□ → *If > 4.5 mark as positive.* →
- 1c. Whiff test
- 1d. Clue cells > 20%.....
- 1e. *Trichomonas vaginalis*.....
- 1f. Buds and/or hyphae (yeast)

Alternate Collection Date

Not done/ Not collected dd MMM yy
□ □□□ □□□□ □□□□

2. PAP SMEAR

- negative for intraepithelial lesion or cancer (malignancy)
- ASC-US
- ASC-H
- SIL-low grade (LSIL)
- SIL-high grade (HSIL)
- AGC
- AGC-favor neoplastic
- cancer

Comments: _____

Pelvic Laboratory Results (PLR-1)

This form is used to document results of specimens collected during the Screening, Enrollment, and follow-up pelvic exams. Record test results on this form as they become available. Fax this form to SCHARP DataFax once results for **all** collected specimens are recorded on this form.

If a test result(s) recorded on this form indicates that the participant has a laboratory-confirmed infection or diagnosis, this infection/diagnosis must be recorded as either a pre-existing condition on the Pre-existing Conditions form (for Enrollment test result(s) only), or an adverse experience on the Adverse Experience (AE) Log (for follow-up visit test result(s) only).

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See Section 14.3.2 of the Study-Specific Procedures Manual for more specific information on assigning visit codes. Note that for regularly scheduled follow-up visits, the visit code is equal to the week on study plus 2.0. For example, the One-week Clinic Visit is assigned a visit code of “03.0,” the Two-week Clinic Visit is assigned a visit code of “04.0,” etc.
- **Initial Specimen Collection Date:** Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. Complete date required.
- **Alternate Collection Date:** This date is to be completed **ONLY** if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form. Complete date required.
- **Results Reporting**
 - If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation on the comments line.
 - If the site lab does not produce test results in the units used on this form, the results must be converted before the laboratory CRF is faxed to SCHARP. Refer to Study Specific Procedures (SSP) for conversion instructions.
- **Item 1:** A vaginal wet prep is required at the One-week, Two-week, and Three-week Clinic Visits, and when clinically indicated. If a vaginal wet prep was performed but not all assays were completed, mark the “Not done” box for each uncompleted wet prep assay. If any and/or all assays were required but not completed, record the reason in the Comments section.
- **Item 1a:** Mark the “positive” box if homogeneous vaginal discharge was observed. If positive, mark “abnormal vaginal discharge” in item 1a of the Screening and Enrollment, Repeat Screening, or Follow-up Pelvic Exam form completed for this pelvic exam.
- **Item 1d:** Mark the “positive” box if more than 20% of cells were clue cells.
- **Item 1e:** Mark the “positive” box if trichomonads were observed.
- **Item 1f:** Mark the “positive” box if yeast buds and/or hyphae were observed.
- **Item 2:** Record the Pap Smear result. Mark only one box. **Note:** *A Pap Smear result is required at the Screening Visit only, and only for those participants who do not have documentation of a normal Pap test result in the 12 calendar months prior to Screening. Only participants with a negative or ASC-US Pap Smear result will be eligible to enroll in the study; participants with an ASC-H, LSIL, HSIL, AGC, AGC-favor neoplastic, or cancer result should not be enrolled in the study.*
 - **negative for intraepithelial lesion or cancer (malignancy):** Includes all normal findings and any findings of infection (trichomonas, candida, etc.), reactive changes/inflammation, glandular changes due to hysterectomy, or atrophic changes.
 - **ASC-US:** Mark this box when abnormal/atypical squamous cells of undetermined significance are reported.
 - **ASC-H:** Mark this box when abnormal/atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion (HSIL) are reported.
 - **SIL-low grade (LSIL):** Mark this box when low-grade squamous interepithelial lesions are reported. This category includes presence of human papillomavirus (HPV) infection, mild dysplasia, and cervical interepithelial neoplasia (CIN 1).
 - **SIL-high grade (HSIL):** Mark this box when high-grade squamous interepithelial lesions are reported. This category includes the presence of moderate to severe dysplasia, carcinoma in situ (CIS), CIN 2, and CIN 3, or changes suspicious for invasive cancer.
 - **AGC:** Mark this box when atypical/abnormal glandular cells are reported. This category includes endocervical (from cervical canal) atypical cells; endometrial atypical cells; glandular atypical cells.
 - **AGC-favor neoplastic:** Mark this box when atypical/abnormal glandular cells that favor cell growth (neoplastic changes) are reported. This category includes endocervical cells and glandular cells.
 - **cancer:** Mark this box when cancer or adenocarcinoma is reported. This includes endocervical, endometrial, extrauterine, and other (not specified) cancers/adenocarcinomas.

SAMPLE. DO NOT FAX
TO DATAFAX

Visit Code

.

1

MTN 004 (136)

SL-1 (151)

Participant ID

- -
Site Number Participant Number Chk

Safety Laboratory Results

Initial Specimen Collection Date

/ /
dd MMM yy

Not done/ Not collected **Alternate Collection Date**
dd MMM yy

1. HEMOGRAM

Not reported

				Severity Grade If applicable	AE Log Page #	Not reportable as an AE
<input type="checkbox"/>	1a. WBC.....	<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/>	$x10^3/mm^3$	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/>	OR <input type="checkbox"/>
<input type="checkbox"/>	1b. Hemoglobin	<input type="text"/> <input type="text"/> . <input type="text"/>	g/dL	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/>	OR <input type="checkbox"/>
<input type="checkbox"/>	1c. Hematocrit.....	<input type="text"/> <input type="text"/> . <input type="text"/>	%			
<input type="checkbox"/>	1d. Platelets	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	$cells/mm^3$	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/>	OR <input type="checkbox"/>
<input type="checkbox"/>	1e. RBC.....	<input type="text"/> . <input type="text"/> <input type="text"/>	$x10^6/mm^3$			

Not done/ Not collected **Alternate Collection Date**
dd MMM yy

2. DIFFERENTIAL

Not reported

		<i>percentage</i>		Absolute Count cells/mm³	Severity Grade If applicable	AE Log Page #	Not reportable as an AE
<input type="checkbox"/>	2a. Neutrophils.....	<input type="text"/> <input type="text"/> . <input type="text"/>	OR	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/>	OR <input type="checkbox"/>
<input type="checkbox"/>	2b. Lymphocytes.....	<input type="text"/> <input type="text"/> . <input type="text"/>	OR	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/> <input type="text"/> <input type="text"/>	OR <input type="checkbox"/>
<input type="checkbox"/>	2c. Monocytes	<input type="text"/> <input type="text"/> . <input type="text"/>	OR	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>			
<input type="checkbox"/>	2d. Eosinophils	<input type="text"/> <input type="text"/> . <input type="text"/>	OR	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>			
<input type="checkbox"/>	2e. Basophils	<input type="text"/> <input type="text"/> . <input type="text"/>	OR	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>			
<input type="checkbox"/>	2f. Bands.....	<input type="text"/> <input type="text"/> . <input type="text"/>	OR	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>			
<input type="checkbox"/>	2g. Atypical lymphocytes..	<input type="text"/> <input type="text"/> . <input type="text"/>	OR	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>			
<input type="checkbox"/>	2h. other, specify:	<input type="text"/> <input type="text"/> . <input type="text"/>	OR	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>			

26-MAR-07

Language

14-30

Staff Initials / Date

Safety Laboratory Results (SL-1)

This form is used to document local safety laboratory results of specimens collected during screening, enrollment, and study follow-up. Record specimen test results on this form as they become available from the local lab. Fax this form to SCHARP DataFax once results for **all** collected specimens are recorded on the form.

If a test result(s) recorded on this form indicates that the participant has a laboratory-confirmed infection or diagnosis, this infection/diagnosis must be recorded as either a pre-existing condition on the Pre-existing Conditions form (for Enrollment Visit test result(s) only), or an adverse experience on an Adverse Experience (AE) Log (for follow-up visit test result(s) only).

Initial Specimen Collection Date: Record the date that the first specimen(s) was collected (NOT the date results were reported or recorded on the form) for this visit. Complete date required.

Alternate Collection Date: This date is to be completed ONLY if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form only when obtained within the same visit window. Complete date required.

Results Reporting

- If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation on the comments line.
- If the site lab does not produce test results in the units used on this form, the results must be converted before the laboratory CRF is faxed to SCHARP. Refer to Study Specific Procedures (SSP) for conversion instructions.
- It may be necessary to round the result reported by the lab up or down to the level of precision allowed on the CRF. For example, a lab-reported hemoglobin value of 11.06 g/dL would be recorded as 11.1 g/dL.
 - If the site lab does not produce test results in the units used on this form, *first* perform the conversion, *then* round the converted result if necessary.
 - If the result reported by the lab has less digits than on the form, fill in “0” for each missing digit. For example a hematocrit value of “42%” would be recorded as “42.0%.”

Severity Grade:

- If any abnormal laboratory values meet the criteria for severity grade 1 or greater, according to the appropriate *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, record the grade in the appropriate box next to the results.
- Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).
- When working with calculated severity grade ranges (e.g., 1.1–1.5 times the site lab upper limit of normal), the calculated range may have more significant digits than the lab result.
 - Treat all missing digits in the lab value as zeros.
 - If the lab value falls between two calculated severity grade ranges, assign it the higher grade.
- There may be situations in which a lab value falls within a site’s lab normal ranges and also within a gradable range per the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*. Per the protocol-specific AE reporting requirements, report this as an AE, as appropriate, and grade it according to the *DAIDS Table*.

AE Log Page #: If the lab value is reportable as an AE, record the page number of the AE Log which is most closely associated with the abnormal lab value.

Not Reportable as an AE: Mark if the lab value is gradable per the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, but is not reportable as an AE. This includes Pre-Existing Conditions and abnormal lab values that do not meet protocol-specific AE reporting requirements.

Item 2: If a differential specimen was collected but results were not reported for all items, mark the “Not reported” box for each result that was not reported. If lab results are available in both percentage and absolute count, absolute count should be recorded on the form.

SAMPLE *DO NOT FAX*
TO DATAFAX

MTN 004 (136)



SL-2 (152)

Visit Code

1

Participant ID

- -
Site Number Participant Number Chk

Safety Laboratory Results

BLOOD CHEMISTRIES

Not done/ Not collected Alternate Collection Date dd MMM yy

3. LIVER FUNCTION TESTS

3a. Alkaline phosphatase U/L OR
3b. AST (SGOT) U/L OR
3c. ALT (SGPT) U/L OR
3d. Total bilirubin . mg/dL OR

Not done/ Not collected Alternate Collection Date dd MMM yy

4. RENAL FUNCTION TESTS

4a. Creatinine . mg/dL OR

Not done/ Not collected Alternate Collection Date dd MMM yy

5. COAGULATION STUDIES

5a. INR..... OR
5b. PTT . seconds OR

Alternate Collection Date

dd MMM yy

6. Plasma *not required* *stored* *not stored* Reason: _____

Comments: _____

Safety Laboratory Results (SL-2)

Initial Specimen Collection Date: Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. Complete date required.

Alternate Collection Date: This date is to be completed ONLY if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form only when obtained within the same visit window. Complete date required.

Results Reporting

- If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation on the comments line.
- If the site lab does not produce test results in the units used on this form, the results must be converted before the laboratory CRF is faxed to SCHARP. Refer to Study Specific Procedures (SSP) for conversion instructions.
- It may be necessary to round the result reported by the lab up or down to the level of precision allowed on the CRF. For example, a lab-reported hemoglobin value of 11.06 g/dL would be recorded as 11.1 g/dL.
 - If the site lab does not produce test results in the units used on this form, *first* perform the conversion, *then* round the converted result if necessary.
 - If the result reported by the lab has less digits than on the form, fill in “0” for each missing digit. For example a hematocrit value of “42%” would be recorded as “42.0%.”

Severity Grade:

- If any abnormal laboratory values meet the criteria for severity grade 1 or greater, according to the appropriate *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, record the grade in the appropriate box next to the results.
- Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).
- When working with calculated severity grade ranges (e.g., 1.1–1.5 times the site lab upper limit of normal), the calculated range may have more significant digits than the lab result.
 - Treat all missing digits in the lab value as zeros.
 - If the lab value falls between two calculated severity grade ranges, assign it the higher grade.
- There may be situations in which a lab value falls within a site’s lab normal ranges and also within a gradable range per the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*. Per the protocol-specific AE reporting requirements, report this as an AE, as appropriate, and grade it according to the *DAIDS Table*.

AE Log Page #: If the lab value is reportable as an AE, record the page number of the AE Log which is most closely associated with the abnormal lab value.

Not Reportable as an AE: Mark if the lab value is gradable per the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, but is not reportable as an AE. This includes Pre-Existing Conditions and abnormal lab values that do not meet protocol-specific AE reporting requirements.

- **Item 6:** Plasma archive is required at the Enrollment and Two-week visits. If a plasma specimen was not collected, mark the “not stored” box and record the reason.

SAMPLE. DO NOT FAX
TO DATAFAX



Visit Code

□□□.□□

1

MTN 004 (136)

SLR-1 (131)

Participant ID

□□□-□□□□□□-□
Site Number Participant Number Chk

STI Laboratory Results

Initial Specimen Collection Date

□□ □□□□ □□
dd MMM yy

Not done/ Not collected Alternat Collection Date dd MMM yy □□□ □□□□ □□□

1. URINE TESTS

Not done 1a. Protein negative or trace 1+ 2+ 3+ 4+ Severity Grade If applicable AE Log Page # □□□ OR Not reportable as an AE

1b. Glucose negative positive
 1c. Blood
 1d. Leukocyte esterase (LE)
 1e. Nitrites

If clinically indicated, perform culture and sensitivity.

1f. Culture negative positive

If positive during follow-up, complete Adverse Experience Log.

Not done/ Not collected Alternat Collection Date dd MMM yy □□□ □□□□ □□□

HIV TEST RESULTS

2. HIV EIA negative positive

If positive, complete HIV Test Results form.

STI Laboratory Results (SLR-1)

*This form is used to document local laboratory results of blood and urine specimens collected at the Screening 1 Visit and when clinically indicated. Record specimen test results on this form as they become available. Fax this form to SCHARP DataFax once results for **all** collected specimens are recorded on this form.*

If a test result(s) recorded on this form indicates that the participant has a laboratory-confirmed infection or diagnosis, this infection/diagnosis must be recorded as either a pre-existing condition on the Pre-existing Conditions form (for Screening/Enrollment test result(s) only), or an adverse experience on the Adverse Experience Log form (follow-up visit test result(s) only).

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See Section 14.3.2 of the Study-Specific Procedures Manual for more specific information on assigning visit codes. Note that for regularly scheduled follow-up visits, the visit code is equal to the week on study plus 2.0. For example, the One-week Clinic Visit is assigned a visit code of “03.0,” the Two-week Clinic Visit is assigned a visit code of “04.0,” etc.
- **Initial Specimen Collection Date:** Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. Complete date required.
- **Alternate Collection Date:** This date is to be completed **ONLY** if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form. Complete date required.
- **Results Reporting**
 - If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation on the comments line.
 - If the site lab does not produce test results in the units used on this form, the results must be converted before the laboratory CRF is faxed to SCHARP. Refer to Study Specific Procedures (SSP) for conversion instructions.
- **AE Severity Grade:** This applies to follow-up visits only. If the visit is a Screening or Enrollment Visit, leave the AE Severity Grade box blank.
 - If any abnormal laboratory values meet the criteria for severity grade 1 or greater, according to the appropriate *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, record the grade in the appropriate box next to the results.
 - Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).
 - When working with calculated severity grade ranges (e.g., 1.1–1.5 times the site lab upper limit of normal), the calculated range may have more significant digits than the lab result.
 - Treat all missing digits in the lab value as zeros.
 - If the lab value falls between two calculated severity grade ranges, assign it the higher grade.
- **Not Reportable as an AE:** Mark if the lab value is gradable per the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, but is not reportable as an AE. This includes Pre-Existing Conditions and abnormal lab values that do not meet protocol-specific AE reporting requirements.
- **AE Log Page #:** This applies to follow-up visits only. If the visit is a Screening or Enrollment Visit, leave the AE Log Page # box blank. If a follow-up visit lab value is reported as and/or associated with an AE, record the page number of the AE Log which is most closely associated with the abnormal lab value.
- **Items 1a–1c:** If clinically indicated, **both** a urine culture and sensitivity are required, per protocol. If there is no clinical indication for performing urine culture and sensitivity, mark the “not done” box for item 1a and proceed to item 2.
- **Item 2:** If the HIV EIA result is positive, conduct Western Blot testing and record the associated test results on the HIV Test Results form.

Note: *A participant must be confirmed HIV uninfected in order to be eligible for study participation.*

SAMPLE. Do NOT FAX TO DATAFAX

MTN 004 (136)



SLR-2 (132)

Visit Code

1

Participant ID

- -
Site Number Participant Number Chk

STI Laboratory Results

3. STI SEROLOGY

3a. Syphilis screening test.....

non-reactive reactive

If non-reactive, go to item 4.

3a1. Syphilis titer 1:

3b. Syphilis confirmatory test

negative positive

If positive, provide treatment. If positive at a Screening Visit, participant is ineligible. If positive during follow-up, complete Adverse Experience Log.

If negative, go to item 4.

3b1. Syphilis titer 1:

Not done/ Not collected Alternat Collection Date dd MMM yy

4. OTHER STI TESTS

4a. N. Gonorrhea

negative positive

4b. C. Trachomatis

If either is positive, provide treatment. If positive at a Screening Visit, participant is ineligible. If positive during follow-up, complete Adverse Experience Log.

Not done/ Not collected Alternat Collection Date dd MMM yy

Comments: _____

STI Laboratory Results (SLR-2)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on page 1 of the form for a given participant and visit.
- **Alternate Collection Date:** This date is to be completed ONLY if the specimen was collected on a different day than the rest of the specimens. A specimen collected for the same visit but on a different day should be recorded on the same form. Complete date required.
- **Results Reporting**
 - If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation on the comments line.
 - If the site lab does not produce test results in the units used on this form, the results must be converted before the laboratory CRF is faxed to SCHARP. Refer to Study Specific Procedures (SSP) for conversion instructions.
- **Item 3:** If the syphilis screening test is reactive, items 3a1 and 3b must be completed.
- **Item 3a1:** Remember to use leading zeros when recording a syphilis titer level. For example, a titer level of 1:20 would be recorded on the form as “1:0020.”
- **Items 3b–4b:** If a result is positive at any time during the study (screening through study exit), provide treatment according to CDC guidelines. If a result is positive at the Screening 1 Visit, the participant is ineligible for study participation. If a result is positive during study follow-up, report the relevant infection(s) as adverse experience(s) on the Adverse Experience Log form, hold study gel, complete a Study Gel Request Slip and mark “hold,” and complete items 1–3 of the Product Hold/Discontinuation form and fax to SCHARP.

SAMPLE *Do NOT FAX TO DATAFAX*



Note: Number pages sequentially (01, 02, 03) for each participant.

Page

MTN 004 (136)

CM-1 (423)

Participant ID

- -
 Site Number Participant Number Chk

Concomitant Medications Log

No medications taken at Screening/Enrollment. _____
 Staff Initials/Date
 ➔ Fax to SCHARP DataFax.

No medications taken throughout study. _____
 Staff Initials/Date
 ➔ End of form. Fax to SCHARP DataFax.

Medication (generic name)										
Indication								Staff Initials/Log Entry Date		
Date Started			Date Stopped			OR <input type="checkbox"/> Continuing at end of study		Taken for a reported AE?		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Dose/Units		Route	PO	IM	IV	TOP	IHL	VAG	REC	other, specify:
		Mark only one.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequency		<input type="checkbox"/> prn	<input type="checkbox"/> qd	<input type="checkbox"/> tid	<input type="checkbox"/> qhs	<input type="checkbox"/> qxh: every	<input type="text"/>	hrs		
		<input type="checkbox"/> once	<input type="checkbox"/> bid	<input type="checkbox"/> qid	<input type="checkbox"/> other, specify: _____					
								Record AE Log page(s):		
		<input type="text"/>		<input type="text"/>						
		<input type="text"/>		<input type="text"/>						

Medication (generic name)										
Indication								Staff Initials/Log Entry Date		
Date Started			Date Stopped			OR <input type="checkbox"/> Continuing at end of study		Taken for a reported AE?		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Dose/Units		Route	PO	IM	IV	TOP	IHL	VAG	REC	other, specify:
		Mark only one.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequency		<input type="checkbox"/> prn	<input type="checkbox"/> qd	<input type="checkbox"/> tid	<input type="checkbox"/> qhs	<input type="checkbox"/> qxh: every	<input type="text"/>	hrs		
		<input type="checkbox"/> once	<input type="checkbox"/> bid	<input type="checkbox"/> qid	<input type="checkbox"/> other, specify: _____					
								Record AE Log page(s):		
		<input type="text"/>		<input type="text"/>						
		<input type="text"/>		<input type="text"/>						

Medication (generic name)										
Indication								Staff Initials/Log Entry Date		
Date Started			Date Stopped			OR <input type="checkbox"/> Continuing at end of study		Taken for a reported AE?		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> yes	<input type="checkbox"/> no	
Dose/Units		Route	PO	IM	IV	TOP	IHL	VAG	REC	other, specify:
		Mark only one.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequency		<input type="checkbox"/> prn	<input type="checkbox"/> qd	<input type="checkbox"/> tid	<input type="checkbox"/> qhs	<input type="checkbox"/> qxh: every	<input type="text"/>	hrs		
		<input type="checkbox"/> once	<input type="checkbox"/> bid	<input type="checkbox"/> qid	<input type="checkbox"/> other, specify: _____					
								Record AE Log page(s):		
		<input type="text"/>		<input type="text"/>						
		<input type="text"/>		<input type="text"/>						

26-MAR-07

Language

Concomitant Medications Log (CM-1)

All medication(s) that are used by the participant during the study, other than study product, must be documented on this form. This includes, but is not limited to, prescription medications, non-prescription (i.e., over-the-counter) medications, preventive medications and treatments (e.g., allergy shots, flu shots, and other vaccinations), herbal preparations, vitamin supplements, naturopathic preparations, and recreational drugs.

- When to fax this form:
 - when pages have been updated or additional Log pages have been completed (only fax updated or new pages);
 - when the participant has completed study participation; and/or
 - when instructed by SCHARP.
- **Page:** Number pages sequentially throughout the study, starting with 01. Do not repeat page numbers. Do not renumber any Concomitant Medications Log pages after faxing, unless instructed by SCHARP.
- **No medications taken at Screening/Enrollment:** Mark this box if no medications were taken by the participant at the time of the Screening or Enrollment visit. Record "Staff Initials/Date."
- **No medications taken throughout study:** Mark this box at the Termination visit if no medications were taken by the participant throughout the entire study. Record "Staff Initials/Date."
- **Medication:** Record the generic name for all medications. For combination medications, record the generic names of the first three main active ingredients.
- **Indication:** For health supplements, such as multivitamins, record "general health." For preventive medications, record "prevention of [insert condition]" (e.g., for flu shot, record "prevention of influenza"). For recreational drugs, record "recreation."
- **Date Started:** If the participant is unable to recall the exact date, obtain participant's best estimate. At a minimum, the year is required.
- **Date Stopped:** At the participant's Termination visit, the "Date Stopped" must be recorded for each medication OR the "Continuing at end of study" box must be marked. At a minimum, the month and year is required.
- **Dose/Units:** If the participant does not know the dose or units, draw a single line through the blank response boxes and initial and date. For prescription combination medications, record the dosage of first three main active ingredients. For multivitamin tablets or liquids, record number of tablets or liquid measurement (e.g., one tablespoon).
- **Route and Frequency:** Below is a list of common route and frequency abbreviations.

Route Abbreviations:

PO oral	IM intramuscular	IV intravenous	TOP topical	IHL inhaled	VAG vaginal	REC rectal
----------------	-------------------------	-----------------------	--------------------	--------------------	--------------------	-------------------

Frequency Abbreviations:

prn as needed	qd every day	tid three times daily	qhs at bedtime
once one time	bid twice daily	qid four times daily	qXH every x hours

- **Taken for a reported AE?:** If the medication was not taken for a reported AE, mark the "no" box and leave the AE Log page boxes blank

SAMPLE: DO NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

Site Number			Participant Number						Chk	

Baseline Medical History

Visit Date

dd		MMM		yy	

	If abnormal, date diagnosed		Description:	Ongoing?									
	normal	abnormal		yes	no								
HEENT	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Lymphatic	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Cardiovascular	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Respiratory	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Liver	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Renal	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Gastrointestinal	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Musculoskeletal	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Neurologic	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
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Skin	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Endocrine/Metabolic	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Hematologic	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Cancer	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Drug allergy	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Other allergy	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Other	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
<p>If yes at the time of enrollment, record on Pre-existing Conditions form. ←</p>													
Alcohol use	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												
Drug use	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1"> <tr> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> <td style="width: 30px; height: 20px;"></td> </tr> <tr> <td>MMM</td> <td>yy</td> <td colspan="2"></td> </tr> </table>					MMM	yy			<input type="checkbox"/>	<input type="checkbox"/>
MMM	yy												

Baseline Medical History – 1 (nonDF)

This form is used to document a participant's baseline medical history, prior to randomization. It is first completed at the Screening 1 Visit. It is then updated at any subsequent screening visits related to the same screening attempt, and updated again at the Enrollment Visit. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Note: *If a participant is being re-screened, a new Baseline Medical History form must be completed as part of the subsequent screening attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

It may be helpful to use a calendar as a probe to help participants recall dates.

Note: *This form should contain information on the participant's medical history through the Enrollment Visit only. Do **not** update this form during follow-up unless the participant recalls additional information related to her medical history at baseline. Be sure to record all conditions that were ongoing at enrollment on the Pre-existing Conditions form.*

Item-specific Instructions:

- **Normal/abnormal:** For each organ system/disease listed, mark the “abnormal” box if there is evidence (either by participant report or by medical records) that the participant has ever experienced any medical problem involving that organ system/disease **since becoming sexually active**. Mark the “normal” box for conditions not reported or documented in medical records.
- **If abnormal, date diagnosed:** For each organ system/disease marked “abnormal,” record the month and year the participant was diagnosed with the condition or began experiencing symptoms.
- **Description:** Provide a description of each reported diagnosis in the space provided.
- **Ongoing?:** For each organ system/disease marked “yes,” determine if the diagnosed condition is ongoing or resolved. Mark the “yes” box if the condition is ongoing (not resolved), and “no” if the condition is resolved. Review all ongoing conditions at the participant's Enrollment Visit. For conditions ongoing at Enrollment, record the condition on the participant's **Pre-existing Conditions** form.
- **Alcohol use:** Record information about the participant's current level of alcohol use.
- **Drug use:** Record information about the participant's current level of recreational drug use.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don't know” or “refused” in the white space next to the response boxes, and initial and date.

SAMPLE: DO NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

			-						-		
Site Number				Participant Number							Chk

Baseline Medical History

Visit Date

dd		MMM			yy

Menstrual History

Usual menstrual cycle: *regular* *irregular*

Usual length of menstrual cycle (days): # of days

Usual number of bleeding days (record range): *minimum* # of days **TO** *maximum* # of days

Age of menarche: years

First day of last menstrual period: } *amenorrheic*
 Last day of last menstrual period: } **OR**

Usual type of menstrual flow (at the heaviest day of menses): *light* *moderate* *heavy*

Usual menstrual symptoms (document type and severity, if any): _____

Usual non-menstrual genital bleeding pattern (document frequency, duration, type of flow, and associated symptoms, if any):

Reproductive history: _____

History of contraception/family planning use: _____

Additional Notes: _____

Baseline Medical History – 2 (nonDF)

Item-specific Instructions:

- **Usual length of menstrual cycle (days):** Record the average number of days between the start dates of two consecutive menstrual cycles. If the participant is amenorrheic, refer to her previous menstrual cycles that occurred prior to the amenorrhea.
- **Usual number of bleeding days:** Record as a range the average number of days (minimum and maximum) the participant reports bleeding during her menses. If the participant is amenorrheic, refer to her previous menstrual cycles that occurred prior to the amenorrhea.
- **Age of menarche:** Record the participant's age of first menstrual period.
- **First day of last menstrual period:** Record the first day of the participant's last menstrual period. Use a calendar to probe for the day, month, and year.
- **Last day of last menstrual period:** Record the last day of the participant's last menstrual period. Use a calendar to probe for the day, month, and year.
- **amenorrheic:** Mark "amenorrheic" if the participant has been without menses for at least the past three cycle intervals or the past six months, whichever is shorter. If "amenorrheic" is marked, leave the "First day of last menstrual period" and "Last day of last menstrual period" boxes blank.
- **Usual menstrual symptoms:** Document the type and severity of any and all reported symptoms the participant commonly experiences in association with her menses. If the participant is amenorrheic, document any usual menstrual symptoms she experienced prior to becoming amenorrheic.
- **Usual non-menstrual genital bleeding pattern:** Document the frequency of bleeding, duration of bleeding, type of flow (e.g., light, moderate, or heavy), and associated symptoms (if any) of any and all reported non-menstrual bleeding commonly experienced by the participant. This includes intermenstrual bleeding (IMB) and/or any breakthrough genital bleeding/spotting associated with the participant's contraceptive use.
- **Reproductive history:** Record the total number, date, and outcome (for example, full-term live birth, premature live birth, spontaneous abortion, etc.) of each of the participant's pregnancies. This should include any gynecologic and obstetrical procedures/surgeries.
- **History of contraception/family planning use:** Record the method(s) of contraception/family planning the participant reports using in the past and currently. If the participant reports current use of hormonal contraception, be sure to record the hormonal contraception on the participant's Concomitant Medications Log.
- **Additional Notes:** Record any necessary or additional information at the bottom of the form.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write "don't know" or "refused" in the white space next to the response boxes, and initial and date.

SAMPLE: DO NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

Site Number			Participant Number						Chk	

History of Genital Symptoms

Visit Date

dd		MMM		yy	

Genital Symptoms	If yes, onset date/ date diagnosed		Description:	Ongoing?		
	yes	no		MMM	yy	yes
Genital sores	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Genital/vaginal itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Genital/vaginal burning	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Genital/vaginal pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pain during sex	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Difficulty when urinating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Burning when urinating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Abnormal or unusual genital/ vaginal discharge	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Unusual genital/ vaginal odor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Abnormal or unusual menstrual cramping (dysmenorrhea)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other genital symptoms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vaginal bleeding or spotting between usual menstrual periods	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
Blood-tinged discharge	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>

If yes to any evaluate for STIs/RTIs. ←

Additional Notes: _____

26-MAR-07

Language

14-44
Staff Initials / Date

History of Genital Symptoms – 1 (nonDF)

This form is used to document a participant's history of genital symptoms at the Screening 1 Visit. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Note: *If a participant is being re-screened, a new History of Genital Symptoms form must be completed as part of the subsequent Screening Attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

It may be helpful to use a calendar as a probe to help participants recall dates.

Note: *Responses to all of the items on this form are based on participant recall at the time of the Screening 1 Visit. Once the participant has completed the Screening Visit, do not make any further updates or changes to the responses recorded on this form.*

Item-specific Instructions:

- **Yes/no:** For each genital symptom listed, mark the “yes” box if the participant reports having experienced that symptom **since becoming sexually active**. Mark the “no” box for symptoms not reported.
- **If yes, onset date/date diagnosed:** For each symptom marked “yes,” record the month and year the participant began experiencing symptoms.
- **Description:** Provide a description of each reported symptom in the space provided.
- **Ongoing?:** For each symptom marked “yes,” determine if the symptom/condition is ongoing or resolved. Mark the “yes” box if the condition is ongoing (not resolved), and “no” if the condition is resolved. If the response is “yes,” evaluate for STIs/RTIs per the protocol and SSP. If the participant is diagnosed with an STI/RTI that is exclusionary per protocol, do **not** enroll the participant. Provide treatment as necessary (per CDC guidelines).

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don't know” or “refused” in the white space next to the response boxes, and initial and date.

SAMPLE *Do NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>
Site Number				Participant Number					Chk

Physical Exam

Exam Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM		yy	

VITAL SIGNS

1. Were vital signs done?..... *yes* *no* → **If no, specify reason in Comments.**

Weight kg BP / mmHg

Height cm Pulse per minute

Oral Temp . °C Respirations per minute

Vital Signs: _____ Staff Initials / Date

FINDINGS

not evaluated *normal* *abnormal* *Item 2 is required. If not evaluated or abnormal, please specify.*

 2. Abdomen _____

Items 3-14 are optional. If abnormal, please specify.

 3. HEENT _____

 4. Neck _____

 5. Lymph Nodes _____

 6. Heart _____

 7. Lungs _____

 8. Extremities _____

 9. Neurological _____

 10. Skin _____

 11. Breast Exam _____

 12. Other, specify: _____

 13. Other, specify: _____

 14. Other, specify: _____

→ **If abnormal and ongoing for any at Enrollment, record on Pre-existing Conditions form. If abnormal during follow-up, update or complete Adverse Experience Log when applicable.**

Findings: _____ Staff Initials / Date

Comments: _____

26-MAR-07

0	1
Language	

14-46

Staff Initials / Date

Physical Exam (nonDF)

This form is used to document the participant's vital signs and physical exam findings. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

***Note:** If a participant is being re-screened, a new Physical Exam form must be completed as part of the subsequent screening attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

Item-specific Instructions:

- **Vital Signs:** When recording weight, height, oral temp, blood pressure (BP), pulse, and respirations, remember to use leading zeros when needed. The staff member who completes these items should initial and date in the space provided.
- **Findings:** The staff member who completes these items should initial and date in the space provided.
- **Item 2:** An abdominal exam is required at the Screening 1, Enrollment, One-week, Two-week, and Three-week Clinic Visits. Record any abnormalities ongoing at enrollment on the participant's **Pre-existing Conditions** form. If abnormal during follow-up, update or complete **Adverse Experience Log** when applicable.
- **Items 3–11:** These items are optional. For each item marked abnormal, specify the reason the organ system was abnormal in the space provided. Record any abnormalities ongoing at enrollment on the participant's **Pre-existing Conditions** form. If abnormal during follow-up, update or complete **Adverse Experience Log** when applicable.
- **Items 12–14:** Use these items to list any additional organ systems that were evaluated. If no other organ systems other than the ones listed in items 1-11 were evaluated, mark items 12–14 as “not evaluated.” Record any abnormalities ongoing at Enrollment on the participant's **Pre-existing Conditions** form. If abnormal during follow-up, update or complete **Adverse Experience Log** when applicable.

SAMPLE. Do NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

Site Number			Participant Number						Chk	

Screening 1 Visit Eligibility

Form Completion Date

dd		MMM		yy	

Complete items 1–3 before the interview.

1. Was the participant willing and able to provide a written informed consent for screening? yes no → **If no, participant is ineligible. End of form.**
2. Was the participant previously enrolled in this study? yes no → **If yes, participant is ineligible. End of form.**
3. Is documentation of a normal Pap test result in the last 12 calendar months available? yes no → **If no, perform Pap test as necessary.**

I am now going to ask you some more questions about yourself. Some of these questions are personal and sensitive, but remember that we do not have your name on these papers and all of your answers will be kept confidential.

4. Have you ever had an adverse or bad reaction to latex (such as latex condoms or gloves)? yes no
5. Has your male sex partner ever had an adverse or bad reaction to latex (such as latex condoms or gloves)? no
6. Have you ever had an adverse or bad reaction to any component of the study product (VivaGel and/or applicator)? no
7. Are you currently using oral and/or vaginal antibiotics or antifungal medications? no
8. Are you breastfeeding? no
9. Do you plan to use a diaphragm, vaginal ring, and/or spermicide for birth control at any time during your study participation? no
10. In the past month (30 days), how many times have you had vaginal sex? By vaginal sex, I mean when a man puts his penis inside your vagina. → **If < 4, participant is ineligible. Go to item 12 on page 2.**

Screening 1 Visit Eligibility – Page 1 (nonDF)

This form is used to document the participant's eligibility for the study at screening. This is a mixed form—some of the items are interviewer-administered (items 4–25), while other items are not (items 1–3 and 26–27). Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

***Note:** If a participant is being re-screened, a new Screening Eligibility form must be completed as part of the subsequent Screening Attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

General Interviewer Tips:

See Section 14.5 of the Study-Specific Procedures Manual for detailed interviewing techniques.

- Help the participant feel comfortable. Develop a rapport or connection with the participant.
- Avoid re-phrasing items, as doing so can change the meaning of the items and make them inconsistent with other interviews.
- Use probes to help the participant remember an answer, clarify a response, or to help report something more accurately.

It is important for you to review the forms for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

***Note:** If the participant provides a response indicating that she is ineligible for the study, continue to administer this form through item 25. Do not inform her that she is ineligible for the study until the form has been administered. Also, refrain from indicating to the participant the reason why she is ineligible, to prevent socially desirable reporting.*

Item-specific Instructions:

- **Items 1–3:** These items are NOT interviewer-administered and should not be read aloud to the participant.
- **Item 2:** Review the Screening and Enrollment Log to verify that the participant has not previously enrolled in the study.
- **Item 3:** Per protocol, a participant must have either a normal Pap test result at screening or documentation of a normal Pap test result in the 12 calendar months prior to screening in order to be eligible to enroll in the study. If the participant does not provide documentation of a normal Pap test result in the 12 calendar months prior to screening, conduct a Pap Smear test for this participant as part of the Screening 1 Visit pelvic exam.

SAMPLE *DO NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number							Chk

Screening 1 Visit Eligibility

11. Do you anticipate having vaginal sex at the same approximate frequency during your study participation? *yes* *no* → **If no, participant is ineligible.**

12. Do you have a regular menstrual cycle that is 21 days or longer? *yes* *no*
 → **If yes, go to item 13.**

12a. Is it because of the birth control you are using, such as Depo-Provera or Norplant? *yes* *no* → **If no, participant is ineligible.**

13. In the past 3 months (90 days), have you given birth, or had a miscarriage or abortion? *yes* *no* → **If no, go to item 14.**

13a. When did you last give birth, have a miscarriage or abortion?

dd MMM yy

↓
If date is within the last 54 days, participant is ineligible. Otherwise, schedule enrollment for when participant is no longer within 90 days of last pregnancy outcome.

14. In the past 3 months (90 days), have you had any gynecological surgery? This would include such procedures as: dilation and curettage (D&C); surgery of the uterus, ovaries, or fallopian tubes, and biopsy or cryotherapy (freezing) of the cervix. *yes* *no* → **If no, go to item 15.**

14a. When did you last have gynecological surgery?

dd MMM yy

↓
If date is within the last 54 days, participant is ineligible. Otherwise, schedule enrollment for when participant is no longer within 90 days of last gynecological surgery.

Screening 1 Visit Eligibility – Page 2 (nonDF)

This form is used to document the participant's eligibility for the study at screening. This is a mixed form—some of the items are interviewer-administered (items 4–25), while other items are not (items 1–3 and 26–27). Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Note: *If a participant is being re-screened, a new Screening Part 1 Visit Eligibility form must be completed as part of the subsequent Screening Attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

General Interviewer Tips:

See Section 14.5 of the Study-Specific Procedures Manual for detailed interviewing techniques.

- Help the participant feel comfortable. Develop a rapport or connection with the participant.
- Avoid re-phrasing items, as doing so can change the meaning of the items and make them inconsistent with other interviews.
- Use probes to help the participant remember an answer, clarify a response, or to help report something more accurately.

It is important for you to review the forms for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

SAMPLE. Do NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

			-					-	
Site Number				Participant Number					Chk

Screening 1 Visit Eligibility

15. In the past 6 months, have you been diagnosed or treated for any sexually transmitted infection, other than genital herpes (HSV) or pelvic inflammatory disease?

yes

no

➔ **If no, go to item 16.**

15a. When were you last diagnosed with or treated for a sexually transmitted infection?

dd		MMM			yy		

If date is within 6 months of enrollment, participant is ineligible. Otherwise, schedule enrollment for when participant is no longer within 6 months of STI diagnosis or treatment.

16. In the past year (12 months), have you used a needle to inject drugs that were not prescribed to you by a medical professional? ...

yes

no

➔ **If no, go to item 17.**

16a. When did you last inject drugs that were not prescribed to you?

dd		MMM			yy		

If date is within 12 calendar months of enrollment, participant is ineligible. Otherwise, schedule enrollment for when participant is no longer within one year of injection drug use.

17. In the past month (30 days), have you participated in any study that uses spermicides, vaginal microbicides, or any other device or drug (including vaccine studies)?

yes

no

➔ **If no, go to item 18.**

17a. When did you last participate in one of these studies?

dd		MMM			yy		

Schedule enrollment when participant is no longer within 30 days of other study participation.

Screening 1 Visit Eligibility – Page 3 (nonDF)

This form is used to document the participant's eligibility for the study. This is a mixed form—some of the items are interviewer-administered (items 4–25), while other items are not (items 1–3 and 26–27). Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Note: *If a participant is being re-screened, a new Screening Eligibility form must be completed as part of the subsequent Screening Attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

General Interviewer Tips:

See Section 14.5 of the Study-Specific Procedures Manual for detailed interviewing techniques.

- Help the participant feel comfortable. Develop a rapport or connection with the participant.
- Avoid re-phrasing items, as doing so can change the meaning of the items and make them inconsistent with other interviews.
- Use probes to help the participant remember an answer, clarify a response, or to help report something more accurately.

It is important for you to review the forms for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

SAMPLE. Do NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

Site Number			Participant Number					Chk		

Screening 1 Visit Eligibility

18. Do you agree to not participate in any study that uses spermicides, vaginal microbicides, or any other device or drug (including vaccine studies) while participating in this study? *yes* *no*
19. From today, through one month after you finish using study products, do you agree to use one of the following types of birth control: Depo-Provera ("the shot"), hormonal contraceptives ("the pill"), Ortho-Evra ("the patch"), an intrauterine device (IUD - inserted at least 30 days prior to enrollment), female sterilization, or have vaginal sex with a male partner who has had a vasectomy?..... *yes* *no*
20. Do you agree to have your partner use study-provided condoms each time you have intercourse during your study participation? *yes* *no*
21. Do you agree to not receive oral or anal sex during your study participation? *yes* *no*
22. From 72 hours before your enrollment through the end of your study participation, do you agree to not use any intravaginal products (other than tampons) or devices, including sex toys? *yes* *no*
23. Are you willing to use the study product, which is VivaGel gel, or VivaGel placebo, or HEC gel twice a day for 14 days? *yes* *no*
24. Are you willing to attend all scheduled study visits? *yes* *no*
25. Are you willing to undergo all study evaluations, including a pelvic exam, colposcopy (when a clinician looks inside your vagina with a magnifying instrument), urine testing, and blood draws? *yes* *no*
- Complete item 26 when Screening 1 urine hCG result is available.**
26. Is the participant pregnant? *yes* *no* **If no to any, participant is ineligible.**
27. Does the participant have any other condition that, in the opinion of the site investigator, would preclude provision or informed consent, make participation in the study unsafe, complicate interpretation of study objectives, or otherwise interfere with achieving study objectives? *yes* *no* **If yes, participant is ineligible.**

Screening 1 Visit Eligibility – Page 4 (nonDF)

This form is used to document the participant's eligibility for the study. This is a mixed form—some of the items are interviewer-administered (items 4–25), while other items are not (items 1–3 and 26–27). Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

***Note:** If a participant is being re-screened, a new Screening Eligibility form must be completed as part of the subsequent Screening Attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

General Interviewer Tips:

See Section 14.5 of the Study-Specific Procedures Manual for detailed interviewing techniques.

- Help the participant feel comfortable. Develop a rapport or connection with the participant.
- Avoid re-phrasing items, as doing so can change the meaning of the items and make them inconsistent with other interviews.
- Use probes to help the participant remember an answer, clarify a response, or to help report something more accurately.

It is important for you to review the forms for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

Item-specific Instructions:

- **Item 19:** If the participant's chosen effective method of contraception is sexual activity with a vasectomized partner, site staff must obtain documentation of the vasectomy in order to enroll the participant.
- **Item 26:** This item is NOT interviewer-administered and should not be read aloud to the participant. Record the Screening 1 Visit urine hCG result here.
- **Item 27:** This item is NOT interviewer-administered and should not be read aloud to the participant. This item should be completed by the site investigator or his/her designee once the Screening 1 Visit has been completed. If, for some reason other than those listed on any of the screening forms, the investigator or designee feels the participant is **not** a good candidate for the study, mark the "yes" box, record the reason in the participant's chart notes, and do not enroll the participant in the study.

SAMPLE *DO NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number							Chk

Clinical Eligibility

Visit Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM		yy	

1. At this visit, was the participant diagnosed by study staff with any of the following sexually transmitted infections (STIs) or reproductive tract infections (RTIs):

- | | yes | no |
|--|--------------------------|--------------------------|
| 1a. chlamydia..... | <input type="checkbox"/> | <input type="checkbox"/> |
| 1b. gonorrhea | <input type="checkbox"/> | <input type="checkbox"/> |
| 1c. syphilis | <input type="checkbox"/> | <input type="checkbox"/> |
| 1d. symptomatic BV | <input type="checkbox"/> | <input type="checkbox"/> |
| 1e. symptomatic candidiasis (yeast)..... | <input type="checkbox"/> | <input type="checkbox"/> |
| 1f. trichomoniasis | <input type="checkbox"/> | <input type="checkbox"/> |
| 1g. chancroid | <input type="checkbox"/> | <input type="checkbox"/> |
| 1h. genital HSV-1 or HSV-2 (active lesions)..... | <input type="checkbox"/> | <input type="checkbox"/> |
| 1i. genital warts of the labia minora, vagina, or cervix, or any other symptomatic genital warts | <input type="checkbox"/> | <input type="checkbox"/> |
| 1j. cervicitis | <input type="checkbox"/> | <input type="checkbox"/> |
| 1k. vaginitis..... | <input type="checkbox"/> | <input type="checkbox"/> |
| 1l. pelvic inflammatory disease (PID) | <input type="checkbox"/> | <input type="checkbox"/> |
| 1m. genital sores or ulcers..... | <input type="checkbox"/> | <input type="checkbox"/> |
| 1n. any other STI or RTI requiring treatment, specify: | <input type="checkbox"/> | <input type="checkbox"/> |

_____ **If yes to any, participant is ineligible. End of form.**

2. At this visit, does the participant have an abnormal physical or pelvic exam finding that, in the opinion of the investigator, would exclude her from the study?

yes	<input type="checkbox"/>
no	<input type="checkbox"/>

If yes, participant is ineligible at this time. End of form.

3. Is the participant in general good health?.....

yes	<input type="checkbox"/>
no	<input type="checkbox"/>

If no, participant is ineligible. End of form.

4. Per clinical judgment of the colposcopist, does visualization of the vaginal and cervical anatomy lend itself to colposcopy?

yes	<input type="checkbox"/>
no	<input type="checkbox"/>

If no, participant is ineligible.

Comments: _____

Clinical Eligibility – Page 1 (nonDF)

This form is completed at the Screening 1 and Enrollment Visits only, and is used to document the participant's clinical eligibility for the study. It is completed at the Screening 1 Visit, and again at the Enrollment Visit. For the Screening 1 Visit, this form is completed once the Screening 1 Visit pelvic exam and wet mount have been conducted, and is completed based on review of the following Screening 1 Visit forms: STI Laboratory Results, Screening and Enrollment Pelvic Exam, History of Genital Symptoms (non-DataFax), and the Baseline Medical History form (non-DataFax). For the Enrollment Visit, this form is completed once the Enrollment Visit pelvic exam and wet mount have been conducted, and is completed based on review of the following Enrollment Visit forms: STI Laboratory Results, Screening and Enrollment Pelvic Exam, Baseline Genital Symptoms, and the Baseline Medical History form (non-DataFax). Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

***Note:** None of the STIs/RTIs listed on this form should be documented on the Pre-existing Conditions form, even if the participant tested positive for one or more of these STIs/RTIs during screening. Because a participant is not eligible for enrollment if she is currently diagnosed with any of these STIs/RTIs, and because the Pre-existing Conditions form only documents ongoing conditions at the time of enrollment, none of the STIs/RTIs recorded on this form should be documented on the Pre-existing Conditions form.*

If a participant is being re-screened, a new Clinical Eligibility form must be completed as part of the subsequent Screening Attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.

Item-specific Instructions:

- **Item 1:** For each STI or RTI listed, record whether the participant is **currently** diagnosed with that STI/RTI.
- **Item 1h:** Record whether the participant **currently** has active HSV-1 or HSV-2 anogenital lesion(s).
- **Item 2:** Record whether the participant **currently** has an abnormal physical or pelvic exam finding that, in the opinion of the investigator, makes her ineligible for study participation. This includes anatomical abnormalities, non-iatrogenic colposcopic findings involving deep epithelial disruption, and women with HPV warts exterior to the labia minora that require treatment.
- **Item 3:** Record whether, in the judgment of the site clinician, the participant's current health status is good.

SAMPLE *DO NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Page 1 of 2

Participant ID

Site Number			Participant Number						Chk	

Screening Summary

Form Completion Date

dd		MMM		yy	

1. Is the participant eligible based on review of all screening data? ^{yes} ^{no}

→ **If yes, end of form.**

2. The participant is ineligible because she: *Mark all that apply.*
 - 2a. is not between the ages of 18 and 24 at screening and enrollment, inclusive
 - 2b. is not able and willing to provide written informed consent to be screened for and to take part in the study
 - 2c. is not in general good health, as determined by the site clinician
 - 2d. is HIV-infected
 - 2e. has an abnormal Pap test result
 - 2f. is not sexually active (has not had vaginal intercourse at least once a week in the 30 days prior to screening)
 - 2g. is unwilling to use an effective method of contraception (as defined in the protocol) during the study
 - 2h. has had an IUD inserted in the 29 days prior to enrollment
 - 2i. is unwilling to undergo all study-related assessments (clinical and laboratory)
 - 2j. is unwilling to adhere to follow-up visit schedule
 - 2k. is unwilling to use VivaGel, VivaGel placebo, or HEC gel as required by the protocol
 - 2l. does not agree to refrain from participation in another study that uses spermicides, vaginal microbicides, or any other device or drug, while enrolled in the study
 - 2m. is unwilling to have partner use study-provided condoms for each act of intercourse while on study
 - 2n. is unwilling abstain from oral-vaginal and penile-anal intercourse
 - 2o. does not have a predictable menstrual cycle
 - 2p. has vaginal and cervical anatomy that does not lend itself to colposcopy
 - 2q. has a history of adverse reaction to latex
 - 2r. has a male sex partner with a history of adverse reaction to latex
 - 2s. is using or plans to use a diaphragm, vaginal ring, and/or spermicide for contraception
 - 2t. used oral and/or vaginal antibiotics or antifungal medications at screening or within 30 days of enrollment

Screening Summary – Page 1 (nonDF)

This form is used to document the participant's eligibility for the study based on the entire screening process. This form is completed once all Screening 1 and Screening 2 Visit evaluations and forms/documentation have been completed and reviewed. If a participant is found to be ineligible at the Screening 1, Screening 2, or Enrollment Visit (prior to randomization), use this form to document the reason(s) the participant was not eligible for study participation. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Note: *If a participant is being re-screened, a new **Screening Summary** form must be completed as part of the subsequent screening attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

Item-specific Instructions:

- **Item 2:** If the participant is NOT eligible for enrollment in the study, *mark all* of the listed reasons that apply:
 - **Item 2a:** Review **Demographics** form, item 1.
 - **Item 2b:** Review **Screening Consent** form, items 2 and 2a; *and* **Enrollment** form, items 1 and 1a.
 - **Item 2c:** Review **Clinical Eligibility** form, item 3, from the Screening 1 and Enrollment Visits.
 - **Item 2d:** Review **STI Laboratory Results** form, item 2 from the Screening 1 Visit, OR if an **HIV Test Results** form is completed at the Screening 1 Visit, review the **HIV Test Results** form, item 5.
 - **Item 2e:** Review **Pelvic Laboratory Results** form, item 2, from the Screening 1 Visit.
 - **Item 2f:** Review **Screening 1 Visit Eligibility** form, item 10.
 - **Item 2g:** Review **Screening 1 Visit Eligibility** form, item 19, and **Screening 2 Visit/Enrollment Eligibility** form, item 11.
 - **Item 2h:** Review **Screening 2 Visit/Enrollment Eligibility** form, item 10.
 - **Item 2i:** Review **Screening 1 Visit Eligibility** form, item 25; *and* **Screening 2 Visit/Enrollment Eligibility** form, item 12.
 - **Item 2j:** Review **Screening 1 Visit Eligibility** form, item 24.
 - **Item 2k:** Review **Screening 1 Visit Eligibility** form, item 23.
 - **Item 2l:** Review **Screening 1 Visit Eligibility** form, item 18.
 - **Item 2m:** Review **Screening 1 Visit Eligibility** form, item 20.
 - **Item 2n:** Review **Screening 1 Visit Eligibility** form, item 21.
 - **Item 2o:** Review **Screening 1 Visit Eligibility** form, items 12 and 12a; *and* **Screening 2 Visit/Enrollment Eligibility** form, items 13 and 13a.
 - **Item 2p:** Review **Clinical Eligibility** form, item 4, from the Screening 1 and Enrollment Visits.
 - **Item 2q:** Review **Screening 1 Visit Eligibility** form, item 4.
 - **Item 2r:** Review **Screening 1 Visit Eligibility** form, item 5.
 - **Item 2s:** Review **Screening 1 Visit Eligibility** form, item 9; *and* **Screening 2 Visit/Enrollment Eligibility** form, item 5.
 - **Item 2t:** Review **Screening 1 Visit Eligibility** form, item 7, *and* **Screening 2 Visit/Enrollment Eligibility** form, item 2.

SAMPLE *DO NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

Site Number			Participant Number						Chk	

Screening Summary

- 2u. has a history of adverse reaction to study product (VivaGel and/or applicator)
- 2v. has a history of prior participation in the study
- 2w. has a Grade 3 or higher laboratory abnormality at screening, and confirmed by retest and/or redraw
- 2x. had a gynecological surgical procedure within 90 days of enrollment
- 2y. is pregnant
- 2z. is within 90 days of last pregnancy outcome at enrollment
- 2aa. has an abnormal physical or pelvic exam finding that is exclusionary, per investigator
- 2ab. is diagnosed with a current STI and/or other RTI requiring treatment according to CDC guidelines
- 2ac. was diagnosed with or treated for an STI (except genital HSV recurrence and PID) within 6 months of enrollment
- 2ad. has a history of non-therapeutic injection drug use in the 12 months prior to enrollment
- 2ae. has participated in another study that uses spermicides, vaginal microbicides, or any other device or drug in the 30 days prior to enrollment
- 2af. is unwilling to abstain from use of other intravaginal products and/or devices (not including tampons)
- 2ag. is breastfeeding
- 2ah. exceeded the 36-day screening window
- 2ai. has any other condition that, in the opinion of the Investigator or designee, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

Screening Summary – Page 2 (nonDF)

Item-specific Instructions:

- **Item 2u:** Review **Screening 1 Visit Eligibility** form, item 6.
- **Item 2v:** Review **Screening 1 Visit Eligibility** form, item 2; *and* Screening and Enrollment Log.
- **Item 2w:** Review **Safety Laboratory Results** form, items 1–5 from the Screening 1 Visit.
- **Item 2x:** Review **Screening 1 Visit Eligibility** form, items 14 and 14a; *and* **Screening 2 Visit/Enrollment Eligibility** form, item 4.
- **Item 2y:** Review **Screening 1 Visit Eligibility** form, item 26; *and* **Screening 2 Visit/Enrollment Eligibility** form, item 14.
- **Item 2z:** Review **Screening 1 Visit Eligibility** form, items 13 and 13a; *and* **Screening 2 Visit/Enrollment Eligibility** form, item 6.
- **Item 2aa:** Review Screening and Enrollment Pelvic Exam forms, items 1 and 2, from both the Screening 1 and Enrollment Visits; **and** the **Clinical Eligibility** forms, item 2, from both the Screening and Enrollment Visits.
- **Item 2ab:** Review **Clinical Eligibility** forms, item 1, from both the Screening and Enrollment Visits.
- **Item 2ac:** Review **Screening 1 Visit Eligibility** form, items 15 and 15a; *and* **Screening 2 Visit/Enrollment Eligibility** form, item 7.
- **Item 2ad:** Review **Screening 1 Visit Eligibility** form, items 16 and 16a; *and* **Screening 2 Visit/Enrollment Eligibility** form, item 9.
- **Item 2ae:** Review **Screening 1 Visit Eligibility** form, items 17 and 17a; *and* **Screening 2 Visit/Enrollment Eligibility** form, item 1.
- **Item 2af:** Review **Screening 1 Visit Eligibility** form, item 22.
- **Item 2ag:** Review **Screening 1 Visit Eligibility** form, item 8; *and* **Screening 2 Visit/Enrollment Eligibility** form, item 3.
- **Item 2ah:** Review **Screening Consent** form, item 2a; *and* date of enrollment as recorded on **Enrollment** form, item 2b.
- **Item 2ai:** Review **Screening 1 Visit Eligibility** form, item 27; **Screening 2 Visit/Enrollment Eligibility** form, item 15.

SAMPLE. Do NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

- -

Site Number Participant Number Chk

**Screening 2 Visit/
Enrollment Eligibility**

Visit Date

/ /

dd MMM yy

To confirm your eligibility for the study, I need to ask you a few more questions.

1. In the past month (30 days), have you participated in any study, or do you plan to participate in any study, that uses spermicides, vaginal microbicides, or any other device or drug (including vaccine studies)? yes no
 2. In the past 30 days, have you used oral and/or vaginal antibiotics or antifungal medications?
 3. Are you breastfeeding?
 4. In the past 3 months (90 days), have you had any gynecological surgery? This would include such procedures as: dilation and curettage (D&C); surgery of the uterus, ovaries, or fallopian tubes, and biopsy or cryotherapy (freezing) of the cervix.
 5. Are you currently using, or do you plan to use a diaphragm, vaginal ring, and/or spermicide for birth control at any time during your study participation?
 6. In the past 3 months (90 days), have you given birth, or had a miscarriage or abortion?
 7. In the past 6 months, have you been diagnosed or treated for any sexually transmitted infection, other than genital herpes (HSV) or pelvic inflammatory disease?
 8. Are you currently using, or do you plan to use any intravaginal products (other than tampons) or devices, including sex toys?
 9. In the past year (12 months), have you used a needle to inject drugs that were not prescribed to you by a medical professional?
 10. Have you had an intrauterine device (IUD) inserted in the past 29 days?
 11. From today through one month after you finish using study products, do you agree to use one of the following types of birth control: Depo-Provera ("the shot"), hormonal contraceptives ("the pill"), Ortho-Evra ("the patch"), an intrauterine device (IUD - inserted at least 30 days prior to enrollment), female sterilization, or have vaginal sex with a male partner who has had a vasectomy? yes no
- ▶ **If yes to any, participant is ineligible.**
▶ **If no, participant is ineligible.**

Screening 2 Visit/Enrollment Eligibility – Page 1 (nonDF)

This form is used to document the participant's eligibility for the study at the Screening 2 Visit. It is an interviewer-administered form. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Note: *If the Enrollment Visit does not take place on the say day as the Screening 2 Visit, all items on this form must be re-assessed on the day of enrollment (prior to enrollment) to confirm participant eligibility. A pregnancy test must be repeated on the day of enrollment (prior to enrollment) and the results should be recorded in the participant chart notes only.*

Note: *If a participant is being re-screened, a new Screening Eligibility form must be completed as part of the subsequent screening attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

General Interviewer Tips:

See Section 14.5 of the Study-Specific Procedures Manual for detailed interviewing techniques.

- Help the participant feel comfortable. Develop a rapport or connection with the participant.
- Avoid re-phrasing items, as doing so can change the meaning of the items and make them inconsistent with other interviews.
- Use probes to help the participant remember an answer, clarify a response, or to help report something more accurately.

It is important for you to review the forms for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

Item-specific Instructions:

- **Items 1–13a:** These items were also asked during the Screening 1 Visit. They must be asked again in order to confirm the participant's eligibility for the study per the inclusion/exclusion criteria stated in the protocol. If the participant provides a response indicating that she is ineligible for the study, continue to administer this form through item 13a. Do not inform her that she is ineligible for the study until the form has been administered. Also, refrain from indicating to the participant the reason why she is ineligible, to prevent socially desirable reporting.
- **Item 11:** If the participant's chosen effective method of contraception is sexual activity with a vasectomized partner, site staff must obtain documentation of the vasectomy in order to enroll the participant.

SAMPLE. Do NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

Site Number			Participant Number						Chk	

**Screening 2 Visit/
Enrollment Eligibility**

Visit Date

dd		MMM			yy		

12. Are you willing to undergo all study evaluations, including a pelvic exam, colposcopy (when a clinician looks inside your vagina with a magnifying instrument), urine testing, and blood draws?

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	→ If no, participant is ineligible.

13. Do you have a regular menstrual cycle that is 21 days or longer?

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	→ If yes, go to statement above item 14.

13a. Is it because of the birth control you are using, such as Depo-Provera or Norplant?

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	→ If no, participant is ineligible.

Complete item 14 when Screening 2 urine HCG result is available.

14. Is the participant pregnant?

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	→ If yes, participant is ineligible.

Complete item 15 after reviewing all Screening forms.

15. Does the participant have any other condition that, in the opinion of the site investigator, would preclude provision or informed consent, make participation in the study unsafe, complicate interpretation of study objectives, or otherwise interfere with achieving study objectives?

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	→ If yes, participant is ineligible.

Screening 2 Visit/Enrollment Eligibility – Page 2 (nonDF)

This form is used to document the participant's eligibility for the study at enrollment. This is a mixed form—some of the items are interviewer-administered (items 1–13a), while other items are not (items 1 and 14–15). Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Note: *If the Enrollment Visit does not take place on the say day as the Screening 2 Visit, all items on this form must be re-assessed on the day of enrollment (prior to enrollment) to confirm participant eligibility. A pregnancy test must be repeated on the day of enrollment (prior to enrollment) and the results should be recorded in the participant chart notes only.*

Note: *If a participant is being re-screened, a new Screening Eligibility form must be completed as part of the subsequent screening attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

General Interviewer Tips:

See Section 14.5 of the Study-Specific Procedures Manual for detailed interviewing techniques.

- Help the participant feel comfortable. Develop a rapport or connection with the participant.
- Avoid re-phrasing items, as doing so can change the meaning of the items and make them inconsistent with other interviews.
- Use probes to help the participant remember an answer, clarify a response, or to help report something more accurately.

It is important for you to review the forms for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

Item-specific Instructions:

- **Item 14:** This item is NOT interviewer-administered and should not be read aloud to the participant. Record the Screening 2 Visit urine hCG result here.
- **Item 15:** This item is NOT interviewer-administered and should not be read aloud to the participant. This item should be completed by the site investigator or his/her designee once the Screening 2 Visit has been completed. If, for some reason other than those listed on any of the screening forms, the investigator or designee feels the participant is **not** a good candidate for the study, mark the “yes” box, record the reason in the participant’s chart notes, and do not enroll the participant in the study.

SAMPLE. Do NOT FAX
TO DATAFAX

MTN 004 (136)



HSR-1 (331)

Visit Code

.

Participant ID

- -
Site Number Participant Number Chk

HSV-2 Culture

Initial Specimen Collection Date

/ /
dd MMM yy

Not done/
Not collected

1. HSV-2 culture.....

negative

positive

Comments: _____

HSV-2 Culture (HSR-1)

This form is used to document HSV-2 culture results of genital (GUD) swabs collected during follow-up. If a test result on this form indicates that a participant has a laboratory-confirmed infection or diagnosis, this diagnosis/infection must be recorded as an adverse experience on the **Adverse Experience (AE) Log**.

Initial Specimen Collection Date: Record the date that the first specimen(s) was *collected* (NOT the date results were reported or recorded on the form) for this visit. Complete date required.

Results Reporting

- If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results and write an explanation on the comments line.

<p>Participant ID</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> </tr> <tr> <td style="text-align: center; font-size: small;">Site Number</td> <td colspan="2" style="text-align: center; font-size: small;">Protocol</td> <td colspan="4" style="text-align: center; font-size: small;">Participant Number</td> <td colspan="3" style="text-align: center; font-size: small;">Chk</td> </tr> </table>											Site Number	Protocol		Participant Number				Chk			<p>Visit Code (Vst)</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> </tr> </table>					<p>Specimen Collection Date</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> <td style="border: 1px solid black; width: 25px; height: 25px;"></td> </tr> <tr> <td colspan="2" style="text-align: center; font-size: small;"><i>dd</i></td> <td colspan="3" style="text-align: center; font-size: small;"><i>MMM</i></td> <td colspan="3" style="text-align: center; font-size: small;"><i>yy</i></td> </tr> </table>									<i>dd</i>		<i>MMM</i>			<i>yy</i>		
Site Number	Protocol		Participant Number				Chk																																			
<i>dd</i>		<i>MMM</i>			<i>yy</i>																																					

# of TUBES (or Specimens)	PRIMARY SPECIMEN TYPE	ADDITIVE	INSTRUCTIONS FOR LAB <small>Unless otherwise noted, enter sub add/derivative code as N/A</small>
<input type="checkbox"/>	Blood (BLD)	EDT (purple top)	At the Enrollment and 2-Week Visits, lab to divide plasma into as many 0.5 mL aliquots as available to store for plasma archive. Store with derivative PL 1/2.
<input type="checkbox"/>	Blood (BLD)	HEP (green top)	At the Enrollment and 2-Week Visits, lab to divide plasma into (2) aliquots of approximately 2.5 mL each for SPL7013 level testing. Store with derivative PL 1/2.
<input type="checkbox"/>	Vaginal Gram Stain Slide (VAG)	NON (no additive)	Re-label with LDMS label. Store duplicate slides (one for on-site storage, and one for shipping and testing at MTN Central Lab). Store with derivative SLD and sub add/derivative GMS.
<input type="checkbox"/>	Cervical Swab (CXS)	PBS	Re-label cryovial with LDMS label. Store with derivative CXS.
<input type="checkbox"/>	Vaginal Swab (VAG)	PAC	Re-label cryovial with LDMS label. Store with derivative SWB.

Comments: _____

Initials: _____ LDMS Data Entry Date:

--	--	--

 /

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 / _____

Sending Staff
Receiving Staff
dd
MMM
yy
LDMS Staff

LDMS Specimen Tracking Sheet (nonDataFax)

This form documents entry of specimens into the Laboratory Data Management System (LDMS). Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

A copy of this form accompanies LDMS specimens (in their original specimen collection containers) to each LDMS entry laboratory. Once the specimens have been entered into LDMS, this form is kept on file at the LDMS entry laboratory. If the site chooses, a copy of this completed form may be made once the specimens have been entered into LDMS and the copy kept in the participant's study notebook. This is not required, however.

Item-specific Instructions:

- **Visit Code:** Record the visit code of the visit at which the LDMS specimens were collected.
- **# of TUBES (or Specimens):** Record the total number of collected tubes or specimens of the listed primary specimen type that will be entered into LDMS. If no LDMS specimens of the primary specimen type were collected, record "0."
- **Initials/Sending Staff:** The clinic staff person who completed the form and/or who is sending the LDMS form and specimens to the LDMS entry lab, records his/her initials here.
- **Initials/Receiving Staff:** The laboratory staff person who received this form (and the LDMS specimens accompanying the form), records his/her initials here.
- **LDMS Data Entry Date:** Record the date the LDMS specimens listed on this form were entered into LDMS.
- **LDMS Staff:** The LDMS laboratory staff person who entered the specimens into LDMS, records his/her initials here.

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code

1

MTN 004 (136)

HTR-1 (351)

Participant ID

- -
Site Number Participant Number Chk

HIV Test Results

Sample 1

1. HIV Western Blot or IFA

Not done/ Not collected Specimen Collection Date
dd MMM yy

negative positive indeterminate

If negative, go to item 5, and contact MTN Central Lab.

If indeterminate, contact MTN Central Lab.

Sample 2

2. HIV Western Blot or IFA

Not done/ Not collected Specimen Collection Date
dd MMM yy

negative positive indeterminate

If positive, go to item 5.

If negative or indeterminate, contact MTN Central Lab.

Sample 3

3. HIV Western Blot or IFA

Not done/ Not collected Specimen Collection Date
dd MMM yy

negative positive indeterminate

Sample 4

4. HIV Western Blot or IFA

Not done/ Not collected Specimen Collection Date
dd MMM yy

negative positive indeterminate

FINAL HIV STATUS

5. Final status: negative positive other, specify: _____

If positive at Screening, participant is ineligible.

Comments: _____

26-MAR-07

0 1
Language

14-70
Staff Initials / Date

HIV Test Results (HTR-1)

This form documents confirmatory HIV test results and final HIV status. This form is completed each time a participant has a positive HIV EIA test result.

*Record specimen test results on this form as they become available from the local lab. Fax this form to SCHARP DataFax once results for **all** required specimens are available and recorded and item 5 has been completed.*

Item-specific Instructions:

- **Visit Code:** The visit code recorded on this form should be the same visit code recorded on the STI Laboratory Results form documenting the positive HIV test result.
- **Specimen Collection Date:** Record the date the specimen was collected (NOT the date results were reported or recorded on the form). For Sample 1, the Specimen Collection Date should be the same date as the collection date of the HIV EIA positive specimen.
- **Not done/Not collected:** Mark this box in the event that a specimen is collected, but a result is not available due to specimen loss or damage. Explain in the Comments section at the bottom of the form why the result is not available.
- **Item 5:** Once a participant's HIV status has been determined, record the final HIV status. If the final HIV status is not clearly negative or clearly positive, mark the "other, specify" box and specify reason(s) on the line provided. If the participant's final HIV status is determined to be positive (according to the protocol testing algorithm) during study follow-up, report the HIV infection as an AE on the AE Log.
- **Comments:** Use this section to document any problems or reasons why expected results are not available; for example, if the sample was lost or damaged.

SAMPLE *Do NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

- -

Site Number Participant Number Chk

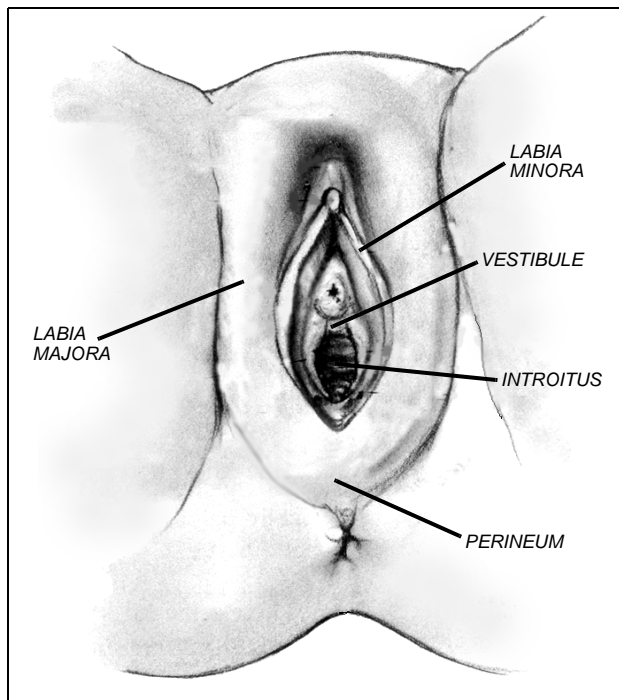
Pelvic Exam Diagrams

no normal variants or abnormal findings observed

Exam Date

dd MMM yy

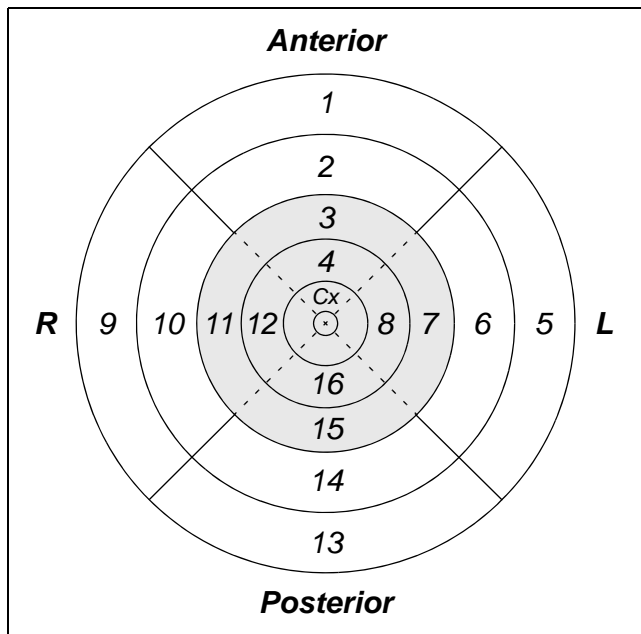
External Genitalia



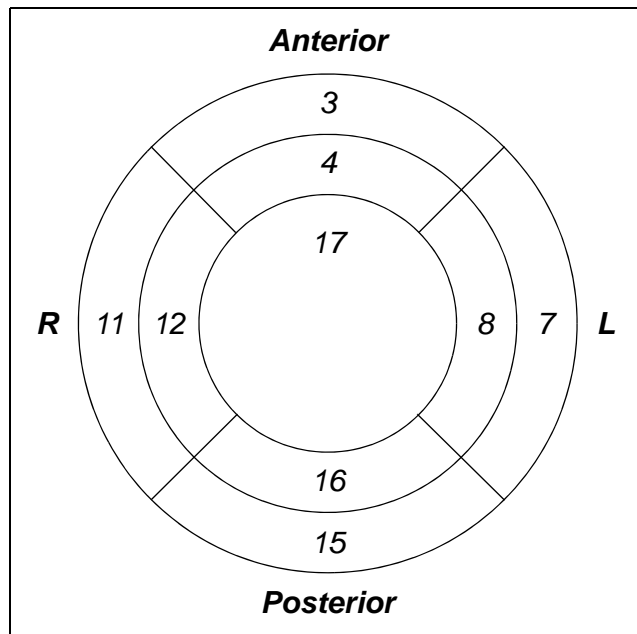
Legend for Vagina/Cervix

1. Anterior vagina, distal half
2. Anterior vagina, proximal half
3. Anterior fornix
4. Cervical trunk, anterior
5. Left lateral vagina, distal half
6. Left lateral vagina, proximal half
7. Left lateral fornix
8. Cervical trunk, left lateral
9. Right lateral vagina, distal half
10. Right lateral vagina, proximal half
11. Right lateral fornix
12. Cervical trunk, right lateral
13. Posterior vagina, distal half
14. Posterior vagina, proximal half
15. Posterior fornix
16. Cervical trunk, post
17. Cervical face

Vagina



Cervix



26-MAR-07

Language

14-72

Staff Initials / Date

Pelvic Exam Diagrams (nonDF)

This form is used to document all variants of normal and all abnormal findings observed during study pelvic exams (screening through study exit). This form is completed each time a pelvic or pelvic/colposcopy exam is performed. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Item-specific Instructions:

- All variants of normal (normal findings) and all abnormal findings must be documented on this form. Variants of normal need only be recorded on this form, and not on any of the DataFax Pelvic Exam forms. The following findings are considered normal variants:
 - anatomic variants
 - mucus retention cysts
 - atrophic changes
 - Nabothian cysts
 - gland openings
 - Gartner's duct cysts
 - skin tags
 - ectopies
- If there are no variants of normal or abnormal findings observed mark the "no normal variants or abnormal findings observed" box.
- Documenting findings on the cervix: If helpful, draw the os in the center of the diagram labeled "Cervix" (lower right corner).

SAMPLE. DO NOT FAX
TO DATAFAX

■ ■ ■ ■ ■ ■ ■ ■ ■ ■ Visit Code

□ □ . □

□ 1 □

MTN 004 (136)

FPM-1 (075)

Participant ID

□ □ □ - □ □ □ □ □ - □
Site Number Participant Number Chk

Family Planning Methods

Visit Date

□ □ □ □ □ □ □ □ □
dd MMM yy

1. Which family planning method or methods is the participant currently using? Mark "none" or all that apply.

- 1a. none
- 1b. vaginal ring
- 1c. spermicide
- 1d. diaphragm
- 1e. sponge
- 1f. intrauterine device (IUD)
- 1g. natural methods such as the withdrawal or rhythm method
- 1h. male condoms
- 1i. female condoms
- 1j. family planning pills or birth control pills
- 1k. injectable contraceptives (such as Depo-Provera)
- 1l. Norplant inserts
- 1m. Ortho Evra/The Patch
- 1n. surgical sterilization (tubal ligation)
- 1o. sex with partner who had a vasectomy
- 1p. other, specify:

Comments: _____

Family Planning Methods (FPM-1)

This form is completed by a site staff member to collect information about the family planning methods that the participant is currently using. It is completed at the Enrollment, One-week, Two-week, and Three-week Clinic Visits.

Item-specific Instruction:

- **Item 1:** Transcribe the family planning methods as documented on the non-DataFax **Baseline Medical History** form for the Enrollment Visit or as documented on the non-DataFax **Follow-up Medical History** form for follow-up visits.

SAMPLE. Do NOT FAX TO DATAFAX



MTN 004 (136)

BGS-1 (030)

Participant ID

Participant ID form with Site Number, Participant Number, and Chk fields.

Baseline Genital Symptoms

Visit Date

Visit Date form with dd, MMM, and yy fields.

1. Since your last study visit, have you experienced any of the following symptoms:

If yes: Are you currently experiencing this symptom?

- 1a. Genital sores?
1b. Genital/vaginal itching?
1c. Genital/vaginal burning?
1d. Genital/vaginal pain?
1e. Pain during sex?
1f. Difficulty when urinating?
1g. Burning when urinating?
1h. Abnormal or unusual genital/vaginal discharge?
1i. Unusual genital/vaginal odor?
1j. Abnormal or unusual menstrual cramping?
1k. Other genital symptoms?

1k1. If yes, specify below.

Local Language: _____

English: _____

- 1l. Vaginal bleeding or spotting between your usual menstrual periods?
1m. Blood-tinged discharge?

Comments: _____

Baseline Genital Symptoms (BGS-1)

This form is interviewer-administered and is used to document genital symptoms reported by the participant at the Enrollment Visit.

Note: *If a participant is being re-screened, a new Baseline Genital Symptoms form must be completed as part of the subsequent screening attempt. See Section 14.3.2 of the Study-Specific Procedures Manual for more instructions regarding re-screening form completion and transmission procedures.*

Interview tips:

See Section 14.5 of the Study-Specific Procedures Manual for detailed interviewing techniques.

- It is important for you to review this form for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

Note: *Responses to all of the items on this form are based on participant recall at the time of the Enrollment Visit. When administering this form, do **not** refer back to the non-DataFax History of Genital Symptoms form. Any clarifications and/or updates to this form should be made during the Enrollment Visit only, unless requested otherwise by SCHARP. Once the participant has completed the Enrollment Visit, do **not** make any further updates or changes to the responses recorded on this form. Record symptoms that are ongoing at the time of enrollment on the Pre-existing Conditions form.*

Item-specific Instructions:

Note: *There is no visit code field on this form since this form is only administered during enrollment.*

- **Item 1:** This item refers to any genitourinary symptoms the participant may have experienced since her last Screening Visit. This may include symptoms that were reported as ongoing at the last Screening Visit. Read each item 1a–1m aloud. For each item marked “yes,” complete the adjacent item, “If yes: Are you currently experiencing this symptom?” For items marked “no,” leave the adjacent item “If yes: Are you currently experiencing this symptom?” blank. For any item 1a–1k marked “yes,” evaluate the participant for STIs/RTIs per the protocol and SSP. If the participant is diagnosed with an STI/RTI that is exclusionary per protocol, do **not** enroll the participant. Provide treatment as necessary (per CDC guidelines).
 - **If yes: Are you currently experiencing this symptom?:** For any item 1a–1m marked “yes” (meaning the condition is ongoing), record the symptom on the Pre-existing Conditions form.
 - **Item 1j:** This item is intended to capture dysmenorrhea reported at baseline.
 - **Item 1k:** If “yes” is marked, record the participant’s verbatim response on the “Local Language” line. If the response is given in a language other than English, provide the English translation on the “English” line.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused” in the white space next to the response boxes, and initial and date.

SAMPLE. Do NOT FAX TO DATAFAX



Note: Number pages sequentially (01, 02, 03) for each participant.

MTN 004 (136)

PRE-1 (012)

Participant ID

Site Number - Participant Number - Chk

Pre-existing Conditions

Form Completion Date

dd MMM yy

No pre-existing conditions reported or observed. End of form. Fax to SCHARP DataFax.

- 1. Description, Date of Diagnosis/Surgery, Comments, Is condition ongoing?
2. Description, Date of Diagnosis/Surgery, Comments, Is condition ongoing?
3. Description, Date of Diagnosis/Surgery, Comments, Is condition ongoing?
4. Description, Date of Diagnosis/Surgery, Comments, Is condition ongoing?
5. Description, Date of Diagnosis/Surgery, Comments, Is condition ongoing?
6. Description, Date of Diagnosis/Surgery, Comments, Is condition ongoing?

Pre-existing Conditions (PRE-1)

This form is used to document the participant's pre-existing medical conditions. Only medical conditions experienced up to study product initiation should be recorded unless otherwise specified in the protocol or Study Specific Procedures (SSPs). Include current medical conditions and any ongoing conditions such as mental illness, alcoholism, drug abuse, and chronic conditions (controlled or not controlled by medication).

- **Page:** Number pages sequentially throughout the study, starting with 01. Do not repeat page numbers. Do not renumber any Pre-existing Conditions pages after faxing, unless instructed by SCHARP.
- **Description:** Whenever possible, provide a diagnosis instead of listing a cluster of symptoms. If no diagnosis is identified, each symptom must be recorded as a separate entry on the Pre-existing Conditions form. If an abnormal lab value is reported, record the lab assay with the direction (i.e., increased or decreased) of the abnormality. For example, "decreased hematocrit" or "increased ALT."
- **Date of Diagnosis/Surgery:** If the participant is unable to recall the date, obtain participant's best estimate. At a minimum, the year is required. If the date is within the same year as study enrollment, the month and year are both required. If the condition is diagnosed due to an abnormal lab result, record the date on which the specimen was collected. If a diagnosis is not available, record the date of onset of condition.
- **Comments:** This field is optional. Use it to record any additional relevant information about the condition.
- **Is condition ongoing?:** Mark "yes" if condition is ongoing at enrollment.
- **Pre-existing Conditions Revisions and Updates:**
 - If a participant recalls a pre-existing condition at a later date, update the form at that time. Refax updated page(s).

SAMPLE. Do NOT FAX TO DATAFAX



MTN 004 (136)

ENR-1 (071)

Participant ID

Site Number			Participant Number						Chk		

Enrollment

Form Completion Date

dd		MMM			yy		

1. Was the participant able and willing to provide written informed consent for enrollment?

yes no → **If no, participant is ineligible. End of form.**

1a. When was the informed consent form for enrollment marked or signed?

dd		MMM			yy	

2. Was a clinic randomization envelope assigned (or a replacement envelope, if a replacement participant)?

yes no → **If no, specify reason in Comments. End of form.**

2a. Envelope number:.....

--	--	--

2b. Date assigned:

dd		MMM			yy	

2c. Time assigned:.....

hr		:	min		24-hour clock

2d. First randomization code:

--	--	--

2e. Second randomization code:

				OR	N/A <input type="checkbox"/>		

If not a replacement participant, go to item 3.

2f. Randomization code of previously enrolled participant:

--	--	--

3. Date study gel dispensed:

dd		MMM			yy	

4. How many cartons of study gel were dispensed?

	# of cartons dispensed
--	------------------------

5. Randomization code of first dispensed carton:.....

--	--	--

6. Randomization code of second dispensed carton:.....

--	--	--

Comments: _____

Enrollment (ENR-1)

This form is used to document a participant's study enrollment/randomization. This form is completed at the Enrollment Visit for participants determined to be eligible for the study. This form is faxed to SCHARP DataFax only if the participant is enrolled (that is, she is assigned a clinic randomization envelope, or a replacement envelope, for replacement participants), and only after completion of the Enrollment Visit.

Item-specific Instructions:

Note: There is no visit code field on this form since this form is only administered at the Enrollment visit.

- **Item 1:** If this item is “no” (the participant is not able and willing to provide written informed consent for enrollment), end the form. Do NOT fax this or any other forms completed for this participant to SCHARP DataFax.
- **Item 2:** If a clinic randomization envelope (or a replacement envelope, if a replacement participant) is not assigned, mark the “no” box and specify in the Comments section the reason an envelope was not assigned, then end the form. Do NOT fax this or any other forms completed for this participant to SCHARP DataFax if an clinic randomization envelope is not assigned.
- **Item 2a:** Record the 3-digit envelope number present on the envelope assigned to this participant.
- **Item 2b:** Record the date the envelope was assigned to the participant. This date should match the “date assigned” recorded for this envelope on the appropriate Envelope Tracking Record and on the study prescription inside the envelope.
- **Item 2c:** Record the time (using a 24-hour clock) when the envelope was assigned to the participant. This time should match the “time assigned” recorded for this envelope on the appropriate Envelope Tracking Record.
- **Item 2d:** Record the first 3-digit randomization code present on the prescription contained in the participant's randomization envelope.
- **Item 2e:** This item is for replacement participants only. Record the second 3-digit randomization code present on the participant's replacement prescription contained inside her replacement envelope. Record the second 3-digit randomization code present on the prescription contained in the participant's randomization envelope.
- **Item 2f:** This item applies only to replacement participants (i.e., participants who enroll in the study to replace previously enrolled, non-adherent participants). Record the first randomization code pre-printed on the prescription of the non-adherent participant who is being replaced.
- **Item 3:** Record the exact day, month, and year the study gel was first dispensed to this participant.
- **Item 4:** Record the number of study gel cartons dispensed to the participant. *NOTE: A standard number of two cartons should be dispensed at the Enrollment Visit. If more than two cartons are dispensed, record the reason why in the Comments section.*
- **Item 5:** From the site pharmacist (or designee), obtain and record the unique 3-digit randomization code present on the carton label of the first carton of study gel dispensed to the participant.
- **Item 6:** From the site pharmacist (or designee), obtain and record the 3-digit randomization code present on the carton label of the second carton of study gel dispensed to the participant.

SAMPLE *DO NOT FAX*
TO DATAFAX

MTN 004 (136)

PK-1 (061) Visit Code

□□□□.□□

□
1

Participant ID

□□□□-□□□□□□-□□
Site Number Participant Number Chk

Pharmacokinetics

Specimen Collection Date

□□□□ □□□□ □□
dd MMM yy

1. Was a blood specimen collected for measuring SPL7013 levels for this participant? *yes* *no*

If no, explain in Comments section. End of form.

2. Participant height: □□□□ *cm*

3. Participant weight:..... □□□□ *kg*

4. Blood draw time: □□□□ : □□□□ *24-hour clock*

Complete item 5 for follow-up visits only.

5. Date and time of last study gel application before this visit:..... □□□□ □□□□ □□□□ □□□□ : □□□□ *24-hour clock*

Comments: _____

Pharmacokinetics (PK-1)

This form is used to document the required Pharmacokinetics (PK) specimen collections at the Enrollment and Two-week Clinic Visits.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See Section 14.3.2 of the Study-Specific Procedures Manual for more specific information on assigning visit codes. Note that for regularly scheduled follow-up visits, the visit code is equal to the week on study plus 2.0. For example, the One-week Clinic Visit is assigned a visit code of “03.0,” the Two-week Clinic Visit is assigned a visit code of “04.0,” etc.
- **Item 1:** If a PK specimen was not collected, mark the “no” box and provide an explanation in the Comments section at the bottom of the form. If the specimen was collected but is not available for testing (i.e., due to specimen loss or damage), mark the “yes” box and provide an explanation in the Comments section at the bottom of the form.
- **Item 4:** Record the time (using a 24-hour clock) when the PK specimen was drawn.
- **Item 5:** Record the date and time of the participant’s last (most recent) application of study gel prior to the PK draw. If specimen is collected at the Enrollment Visit, leave this item blank.

SAMPLE. DO NOT FAX TO DATAFAX

MTN 004 (136)



FV-1 (121)

Visit Code .

Participant ID

- -
Site Number Participant Number Chk

Follow-up Visit

Visit Date

dd MMM yy

1. hCG for pregnancy: *not done* *negative* *positive*
1a. Specify reason(s): *not done* *negative* *positive*
_____ **If positive, complete Pregnancy Report and History form and Product Hold/Discontinuation form.**

2. Were any new adverse experiences reported at this visit? *yes* *no* **If no, go to item 3.**

2a. How many **new** AE Log pages were completed for this visit? # of pages

3. At this visit, how many **unused** applicators did the participant return? # of **unused** applicators returned

4. **NO LONGER APPLICABLE FOR THIS PROTOCOL.** applicators did the participant return? **NO LONGER APPLICABLE FOR THIS PROTOCOL.** # of **unused** applicators returned

5. At this visit, how many cartons of study gel were dispensed to the participant? # of cartons dispensed **If 0, end of form.**

5a. Randomization code of first dispensed carton:

5b. Randomization code of second dispensed carton: OR N/A

Comments: _____

Follow-up Visit (FV-1)

This form is used to document the required (regularly scheduled) One-week, Two-week, and Three-week Clinic follow-up visits. It is completed at each regularly scheduled follow-up visit, regardless of whether the visit is conducted within the protocol-specified window or made up outside the visit window.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See Section 14.3.2 of the Study-Specific Procedures Manual for more specific information on assigning visit codes. Note that for regularly scheduled follow-up visits, the visit code is equal to the week on study plus 2.0. For example, the One-week Clinic Visit is assigned a visit code of “03.0,” the Two-week Clinic Visit is assigned a visit code of “04.0,” etc.
- **Item 1:** Record the hCG urine pregnancy test result. If a urine pregnancy test result is not available (specimen not collected and/or test not done), mark the “not done” box and complete item 1a. *Note: A Pregnancy Report and History form must be completed for each pregnancy.* Once a participant tests positive for hCG urine pregnancy and a Pregnancy Report and History form (PR-1) has been completed for this pregnancy, subsequent positive pregnancy test results should not be recorded on a new PR-1 unless they represent a new pregnancy.
- **Item 1a:** Specify the reason(s) why the required pregnancy test was not done.
- **Item 2:** Mark the “yes” box if a new (previously unreported) AE is reported or observed at this visit. If the box is marked “yes,” record in item 2a how many **new** AE Log pages were completed for this visit. For example, if two new AEs were reported, record “02.” Note that the Visit Code recorded in item 10 of these two AE Log pages should be the same as the Visit Code recorded on this form.
- **Item 3:** Record the number of **unused** study gel applicators the participant returned at this visit only.
- **Item 5:** Record the number of cartons of study gel given to the participant at this visit. This will be the same amount documented on the **Study Gel Request Slip** (and/or on the **Replacement Prescription**, if replacement carton(s) are also dispensed), unless documentation from the pharmacy staff states otherwise.
- **Item 5a:** From the site pharmacist (or designee), obtain and record the unique 3-digit randomization code present on the carton label of the first carton of study gel dispensed to the participant at this visit.
- **Item 5b:** From the site pharmacist (or designee), obtain and record the unique 3-digit randomization code present on the carton label of the second carton of study gel dispensed to the participant at this visit. If a second carton was not dispensed at this visit, mark the “N/A” box.

SAMPLE. Do NOT FAX
TO DATAFAX

MTN 004 (136)



SGA-1 (173)

Visit Code

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number						Chk	

Study Gel Adherence

Visit Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
dd		MMM			yy		

I know that you are counseled to insert the study gel in the morning and in the evening each day, but I also know that this is not always possible.

1. Since your last regularly scheduled study visit, how many applicators have you used? # applicators

2. Since your last regularly scheduled study visit, was there ever a day in which you used the study gel less than two times? *yes* *no* → **If no, end of form.**

2a. How many days did you use the study gel less than two times? # days

Comments: _____

Study Gel Adherence (SGA-1)

This form is used to collect information on study gel adherence from study participants. This is an interviewer-administered form, and it is administered at the one-week and two-week clinic visits. Note: If the participant misses her two-week clinic visit, administer this form at her three-week clinic visit.

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **Item 2a:** Record the total number of days since the participant's last regularly scheduled visit that she reports using the study gel less than twice a day. The number of days reported should not exceed the number of days since the participant's last regularly scheduled visit.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write "don't know" or "refused," and initial and date the note in the white space next to the item.

SAMPLE Do NOT FAX TO DATAFAX



Visit Code [][] . []

1

MTN 004 (136)

FGS-1 (130)

Participant ID

[][][] - [][][][][] - []
Site Number Participant Number Chk

Follow-up Genital Symptoms

Visit Date

[][] [][][] [][]
dd MMM yy

1. Since your last study visit, have you experienced any of the following symptoms:

If yes: When did you first experience this symptom?

Continuing from previous visit

Table with columns: Symptom, yes, no, dd, MMM, yy, OR, Continuing from previous visit. Rows include: 1a. Genital sores?, 1b. Genital/vaginal itching?, 1c. Genital/vaginal burning?, 1d. Genital/vaginal pain?, 1e. Pain during sex?, 1f. Difficulty when urinating?, 1g. Burning when urinating?, 1h. Abnormal or unusual genital/vaginal discharge?, 1i. Unusual genital/vaginal odor?, 1j. Abnormal or unusual menstrual cramping?, 1k. Other genital symptoms?.

1k1. If yes, specify below.

Local Language: _____

English: _____

If yes to any, conduct pelvic exam if clinically indicated. Update or complete Adverse Experience Log when applicable.

Table with columns: Symptom, yes, no, dd, MMM, yy, OR, Continuing from previous visit. Rows include: 1l. Vaginal bleeding or spotting between your usual menstrual periods?, 1m. Blood-tinged discharge?.

If yes to any, complete Genital Bleeding Assessment form if indicated. Conduct pelvic exam if indicated.

Comments: _____

Follow-up Genital Symptoms (FGS-1)

This form is interviewer-administered, and is used to document genital symptoms reported by the participant during study follow-up. It is completed at each regularly scheduled follow-up visit (the One-week, Two-week, and Three-week Clinic Visits).

Interview tips:

See Section 14.5 of the Study-Specific Procedures Manual for detailed interviewing techniques.

- It is important for you to review this form for accuracy and completeness once the interview is complete. By reviewing the form briefly while the participant is still there, you can go back to an item that may have accidentally been skipped.

Note: Responses to all of the items on this form are based on participant recall at the time the form is being administered. When administering this form, **do not** refer back to previously completed Genital Symptoms forms (Baseline and Follow-up). Any clarifications and/or updates to this form should be made only during the visit in which this form is completed, unless requested otherwise by SCHARP. Once the participant has completed the visit, do not make any further updates or changes to the responses recorded on this form. If, at a subsequent study visit, the participant reports additional symptoms she experienced at baseline, or at a time point covered by a previous Follow-up Genital Symptoms form, do **not** update any of the previously completed forms. Instead, record the new information on the current Follow-up Genital Symptoms form and explain the discrepancy in both the Comments section and/or in the participant's chart notes. If the participant reports additional symptoms that were ongoing at enrollment, record these on the Pre-existing Conditions form.

Once the interview is complete, review the completed Genital Symptoms form (Baseline or Follow-up) from the previous visit and identify any symptoms that were a) reported as ongoing, and b) documented on an AE Log. If the same symptoms are reported as not present at the current visit (response on current visit's Follow-up Genital Symptoms form is "no"), query the participant for an outcome date and record this in item 6a of the associated AE Log.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See Section 14.3.2 of the Study-Specific Procedures Manual for more specific information on assigning visit codes. Note that for regularly scheduled follow-up visits, the visit code is equal to the week on study plus 2.0. For example, the One-week Clinic Visit is assigned a visit code of "03.0," the Two-week Clinic Visit is assigned a visit code of "04.0," etc.
- **Item 1:** Read each item 1a-1m aloud. For any item marked "yes," conduct a pelvic exam if clinically indicated (and not already required for the visit). For each item marked "yes," complete an Adverse Experience (AE) Log if this is the **first** time the symptom is reported since the participant enrolled in the study. If this is **not** the first time the condition has been reported since enrollment, an AE Log should already have been completed for this condition—review the previously completed AE Log and either update any relevant information, or complete a new AE Log as necessary (e.g., in cases where a previously reported AE has increased in severity or frequency). If the symptom was first reported on the participant's Baseline Genital Symptoms and Pre-existing Conditions forms and it has not increased in severity or frequency, **do not** complete an AE Log—do record on this form that the condition has not increased in severity or frequency since enrollment/baseline.
- **Item 1j:** This item is intended to capture dysmenorrhea reported during follow-up visits. If the participant reports dysmenorrhea and/or any other symptom(s) related to menstruation, probe for further information (i.e., type and severity of symptoms), then compare to participant's usual baseline menstrual symptoms (as documented on the non-DataFax Baseline Medical History form and Baseline Genital Symptoms form) to determine whether an AE should be reported.
- **Item 1k:** If "yes" is marked, record the participant's verbatim response on the "Local Language" line. If the response is given in a language other than English, provide the English translation on the "English" line.
- **If yes: When did you first experience this symptom?:** For each item marked "yes," record the day, month, and year the participant first began experiencing symptoms; if necessary, use a calendar to probe. If the participant provides a date that is prior to the date of the previous visit, mark "continuing from previous visit" and leave the day, month, and year boxes blank. If the participant states that a symptom began on the exact date of the previous visit, clarify whether or not the symptom was present at the time the visit occurred. If she states that the symptom was present during the previous visit, mark "Continuing from previous visit" and leave the day, month, and year boxes blank. If the participant states that the symptom occurred on the same day as the previous visit, but after she had completed the visit, record the day, month, and year of the previous visit and leave the "continuing from previous visit" box blank.
- **Continuing from previous visit:** Mark this box for symptoms reported as continuing since the time of the previous visit. If this box is marked, leave the "If yes: When did you first experience symptoms?" boxes blank. If a date is recorded, leave the corresponding "continuing from previous visit" box blank.

Items 1l–1m: If the participant reports vaginal bleeding or spotting between usual menstrual periods, or any blood-tinged genital/vaginal discharge, refer to Section 10 of the Study-Specific Procedures Manual and protocol Appendix II.

SAMPLE Do NOT FAX TO DATAFAX



Visit Code

Form boxes for Visit Code

Form box with number 1

MTN 004 (136)

FPE-1 (165)

Participant ID

Form boxes for Participant ID: Site Number, Participant Number, Chk

Follow-up Pelvic Exam

Exam Date

Form boxes for Exam Date: dd, MMM, yy

1. Naked eye, speculum, and bimanual exam assessments: not done, no abnormal findings, abnormal findings. If not done, specify reason in Comments on page 3. End of form. If no abnormal findings, go to item 9 on page 2.

1a. Abnormal non-colposcopic findings: Mark all that apply.

- 1a1. enlarged/tender inguinal lymph nodes
1a2. abnormal vaginal discharge
1a3. abnormal cervical discharge
1a4. blood-tinged discharge
1a5. blood in vagina—no identified source
1a6. blood from cervical os
1a7. bleeding from site of epithelial disruption
1a8. erythema
1a9. ulceration
1a10. laceration
1a11. abrasion
1a12. peeling
1a13. petechia
1a14. ecchymosis
1a15. vesicles
1a16. edema
1a17. abnormal cysts
1a18. grossly white finding
1a19. mass
1a20. warts—on and/or interior to labia minora
1a21. warts—exterior to labia minora
1a22. adnexal tenderness
1a23. cervical motion tenderness
1a24. uterine tenderness
1a25. other abnormal findings, specify:

If finding is new, complete Adverse Experience Log as applicable.

- 2. Do any of these exam findings involve generalized erythema or severe edema...?
3. Do any of these exam findings involve deep epithelial disruption (ulceration)?
3a. Was the deep epithelial disruption (ulceration) observed in more than one distinct area?
4. Do any of these exam findings involve presumed cervicitis?
5. Do any of these exam findings involve superficial epithelial disruption (abrasion/peeling)?
6. Do any of these exam findings involve disrupted blood vessels?
6a. Were disrupted blood vessels observed in more than one distinct area?

Follow-up Pelvic Exam (FPE-1)

This form, along with the non-DataFax Pelvic Exam Diagrams, is used to document the pelvic (and, when applicable, colposcopy) exams conducted during study follow-up.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See Section 14.3.2 of the Study-Specific Procedures Manual for more specific information on assigning visit codes. Note that for regularly scheduled follow-up visits, the visit code is equal to the week on study plus 2.0. For example, the One-week Clinic Visit is assigned a visit code of “03.0,” the Two-week Clinic Visit is assigned a visit code of “04.0,” etc.
- **Item 1:** A pelvic exam is required at the One-week, Two-week, and Three-week Clinic Visits, and when clinically indicated. Document only those abnormal findings observed during naked eye, speculum, and bimanual examination. If a pelvic exam was required but not done, mark the “not done” box and record the reason the required pelvic exam was not done in the Comments section at the bottom of page 3. If no abnormal findings are observed, mark the “no abnormal findings” box, leave item 1a blank and go to item 9. If one or more abnormal findings are observed, mark the “abnormal findings” box and continue to item 1a.
- **Item 1a:** Mark the box to the left of **each** abnormal finding observed via naked eye, speculum, and bimanual examination **only**. If an observed abnormal finding is not listed, mark the “other abnormal findings, specify” box and describe the abnormal finding in the space provided.
- **Items 1a2, 1a8, and 1a16:** If abnormal vaginal discharge, erythema, or edema are observed, refer to protocol Appendix II.
- **Items 2–6:** If the response to any of these items is “yes,” refer to protocol Appendix II for further instructions on study gel use and clinical follow-up. These questions refer to the abnormal findings documented in item 1a. They do **not** include abnormal findings observed by colposcopy only.

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code

1

MTN 004 (136)

FPE-2 (166)

Participant ID

- -
Site Number Participant Number Chk

Follow-up Pelvic Exam

7. Was unexpected genital bleeding observed (that is **not** associated with an abnormal exam finding)?

yes no

If yes, refer to protocol Appendix II. Complete Genital Bleeding Assessment form.

8. Do any pelvic exam findings from this visit warrant a product hold?.....

yes no

If yes, complete Product Hold/Discontinuation form.

9. Colposcopic exam assessment: *Required at Two-week Clinic Visit.*

not done no abnormal findings abnormal findings

9a. Abnormal **colposcopic** findings: *Mark all that apply.*

If not done OR no abnormal findings, go to item 10 on page 3.

- 9a1. abnormal vaginal discharge
- 9a2. abnormal cervical discharge
- 9a3. blood-tinged discharge
- 9a4. blood in vagina—no identified source
- 9a5. blood from cervical os
- 9a6. bleeding from site of epithelial disruption
- 9a7. erythema
- 9a8. ulceration
- 9a9. laceration
- 9a10. abrasion
- 9a11. peeling
- 9a12. petechia
- 9a13. ecchymosis
- 9a14. vesicles
- 9a15. edema
- 9a16. abnormal cysts
- 9a17. grossly white finding
- 9a18. mass
- 9a19. warts—on and/or interior to labia minora
- 9a20. warts—exterior to labia minora
- 9a21. other abnormal findings, specify:

Follow-up Pelvic Exam (FPE-2)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on page 1 of this form for a given participant and visit.
- **Items 7–8:** If the response to either of these items is “yes,” refer to protocol Appendix II for further instructions on study gel use and clinical follow-up. These questions refer to the abnormal findings documented in item 1a. They do **not** include abnormal findings observed by colposcopy only.
- **Item 9:** Colposcopy is required at the Two-week Clinic Visit, and when clinically indicated. Document any abnormal findings observed during colposcopic examination **only**. If the exam did not include colposcopy, mark the “not done” box, leave item 9a blank and go to item 2. If colposcopy was required but not done, also record the reason the required colposcopy was not done in the Comments section at the bottom of page 3. If no abnormal findings are observed, mark the “no abnormal findings” box, leave item 9a blank and go to item 2. If one or more abnormal findings are observed, mark the “abnormal findings” box and continue to item 9a. Note: Abnormal findings observed by colposcopy only are not reportable as AEs.
- **Item 9a:** Mark the box to the left of **each** abnormal finding observed on colposcopy **only**. If an observed abnormal finding is not listed, mark the “other abnormal findings, specify” box and describe the abnormal finding in the space provided.

SAMPLE *DO NOT FAX*
TO DATAFAX



Visit Code

MTN 004 (136)

FPE-3 (167)

Participant ID

- -
Site Number Participant Number Chk

Follow-up Pelvic Exam

10. Cervical Ectopy: Percentage of cervical surface area.

0% 1-25% 26-50% 51-75% > 75%

naked eye *colposcopy*

10a. Cervical ectopy assessed by:

Alternate Collection Date

dd *MMM* *yy*

not required *stored* *not stored* *Reason:*

11. Gram stain (vaginal) → _____

12. Cervical swabs..... → _____

13. GUD swab(s) → _____
of swabs ←

14. Vaginal swab..... → _____

Comments: _____

Follow-up Pelvic Exam (FPE-3)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on page 1 of this form for a given participant and visit.
- **Items 10 and 10a:** When colposcopy is performed, cervical ectopy must be assessed by colposcopy and not by naked eye. If colposcopy is not performed, item 10a should be marked “naked eye.”
- **Items 11–14:** Record the alternate collection date when the specimen(s) was *collected* for this visit if the date is not the same as the Exam Date (NOT the date results were reported or recorded on the form). Complete date required.
- **Item 11:** Collection of a vaginal Gram Stain smear (duplicate slides) is required as part of the One-week, Two-week, and Three-week Clinic Visit pelvic exams. If a vaginal Gram Stain smear was not collected at one of these visits, mark the “not stored” box and record the reason.
- **Item 12:** Collection of cervical swabs for cytokine and innate factor testing is required as part of the One-week, Two-week, and Three-week Clinic Visit pelvic exams. If cervical swabs were not collected at one of these visits, mark the “not stored” box and record the reason.
- **Item 13:** A multiplex PCR swab for genital ulcer disease (GUD) is collected at the One-week, Two-week, and Three-week Clinic Visits for each genital ulcer, cluster of ulcers, and/or other anogenital finding thought to be Herpetic. If one or more swabs are collected, mark the “stored” box and record the number of swabs collected. If no swab collection is warranted, mark the “not required” box. If a genital ulcer, cluster of ulcers, and/or other potentially Herpetic anogenital finding is observed, but no swab is collected, mark the “not stored” box and record the reason.
- **Item 14:** Collection of a vaginal swab for quantitative culture is required as part of the One-week, Two-week, and Three-week Clinic Visits. If a vaginal swab was not collected at one of these visits, mark the “not stored” box and record the reason.
- **Comments:** Record any necessary or additional information at the bottom of the form.

SAMPLE *Do NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Page 1 of 2

Participant ID

Site Number			Participant Number						Chk	

Follow-up Medical History

Visit Date

dd		MMM		yy	

Since the last study visit, has the participant experienced any new conditions or changes in previously reported conditions (improvement or worsening)? ... *yes* *no*

→ If no, go to page 2.

			<i>If abnormal, onset date:</i>			<i>OR continuing from previous</i>	<i>Description:</i>
	<i>normal</i>	<i>abnormal</i>	<i>dd</i>	<i>MMM</i>	<i>yy</i>	<i>visit</i>	
HEENT	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Lymphatic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Cardiovascular	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Respiratory	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Liver	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Renal	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Gastrointestinal	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Musculoskeletal	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Neurologic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Skin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Endocrine/Metabolic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Hematologic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Drug allergy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Other allergy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
→ If abnormal, update or complete Adverse Experience Log when applicable.							
Alcohol use	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____
Drug use	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	_____

Follow-up Medical History – 1 (nonDF)

This form is used to document a participant's follow-up medical history during the study (that is, her medical history since her last study visit). It is completed at each regularly scheduled follow-up visit (the One-week, Two-week, and Three-week Clinic visits). Because this form is a non-DataFax form, this form should not be faxed to SCHARP DataFax.

It may be helpful to use a calendar as a probe to help participants recall dates.

If you need additional space for notation, use the space provided at the bottom of page 2.

Note: *Each Follow-up Medical History form should contain medical information reported by the participant at the time the form was completed. If, at a subsequent study visit, the participant reports additional medical information related to the time period covered on a previous Follow-up Medical History form, **do not** update the previous form. Instead, record the new information on the current Follow-up Medical History form and explain the discrepancy in the "Additional Notes" section (may be documented in the participant's chart notes as well). If the participant reports additional medical information related to her baseline medical history, do update the Baseline Medical History (non-DataFax) form, and the Pre-Existing Conditions form (for conditions present at enrollment).*

Item-specific Instructions:

- **Normal/abnormal boxes:** The first time this form is completed for a participant (at her first follow-up visit), review the participant's **Pre-existing Conditions** form. For each ongoing condition, review the condition with the participant and record updated information about the condition on this form. For all visits after the first follow-up visit, review the **Follow-up Medical History** form completed at the previous visit and record updated information on all conditions that were ongoing at the last visit on the **Follow-up Medical History** form for the current visit.
- **If abnormal, onset date:** For each item marked "abnormal," record the day, month, and year the participant was diagnosed with the condition. When applicable, complete an **Adverse Experience Log** for the condition recording this date as the AE Onset Date (item 2 of the **Adverse Experience Log** form).
- **Continuing from previous visit:** Mark this box for items that are continuing from a previous visit (that is, the onset date of the condition is recorded on a previously-completed medical history form). If this box is marked, leave the "If abnormal, onset date" boxes blank. If an onset date is recorded, leave the "continuing from previous visit" box blank.
- **Description:** Provide a description of each observed/reported condition in the space provided. Provide a diagnosis along with reported symptoms whenever possible. If the condition is continuing from a previous visit, use the same text to describe the condition.
- **Alcohol use:** Record information about the participant's current level of alcohol use. If there have been no changes since the previous visit record "no changes."
- **Drug use:** Record information about the participant's current level of drug use. If there have been no changes since the previous visit record "no changes."
- **If abnormal to any, update or complete Adverse Experience Log when applicable:** For each item marked as "abnormal," complete an **Adverse Experience (AE) Log** form if this is the **first** time the condition has been reported since the participant enrolled in the study. If this is **not** the first time the condition has been reported since enrollment, an **AE Log** form should already have been completed for this condition—review the previously completed **AE Log** form and either update any relevant information, or complete a new AE Log form as necessary (e.g., in cases where a previously reported AE has increased in severity or frequency). If the condition was first reported on the participant's **Baseline Medical History** and **Pre-existing Conditions** forms and it has not increased in severity or frequency, **do not** complete an **AE Log** form—do record on this form that the condition has not increased in severity or frequency since enrollment/baseline.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write "don't know" or "refused" in the white space next to the boxes, and initial and date.

SAMPLE *DO NOT FAX TO DATAFAX*

Not a DataFax form. Do not fax to DataFax.

MTN 004 (136)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number							Chk

Follow-up Medical History

Visit Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<i>dd</i>		<i>MMM</i>			<i>yy</i>

Menstrual Information

	<i>dd</i>	<i>MMM</i>	<i>yy</i>	} → <i>amenorrheic</i> OR <input type="checkbox"/>
First day of last menstrual period:	<input type="text"/>	<input type="text"/>	<input type="text"/>	
Last day of last menstrual period:	<input type="text"/>	<input type="text"/>	<input type="text"/>	

Reproductive history: _____

History of contraception/family planning use: _____

Additional Notes: _____

Follow-up Medical History – 2 (nonDF)

Item-specific Instructions:

- **Menstrual Information**
 - **First day of last menstrual period:** Record the first day of the participant's last menstrual period. Use a calendar to probe for the day, month, and year.
 - **Last day of last menstrual period:** Record the last day of the participant's last menstrual period. Use a calendar to probe for the day, month, and year.
 - **Amenorrheic:** Mark "amenorrheic" if the participant has been without menses for at least the past three menstrual cycles or the past six months, whichever is shorter. If "amenorrheic" is marked, leave the "First day of last menstrual period" and the "Last day of last menstrual period" boxes blank and provide a response to the question, "If amenorrheic, is it due to an unexpected or unknown cause?" Amenorrhea that occurs during study follow-up (in other words, is not present at baseline), should be reported as an adverse experience on an AE Log form if it is due to an unexpected or unknown cause.
- **Reproductive History:** Record any relevant information on the participant's pregnancy or reproductive history since her last follow-up visit.
- **Additional Notes:** Record any necessary or additional information at the bottom of the form.

SAMPLE: Do NOT FAX TO DATAFAX



Note: Number pages sequentially (001, 002, 003) for each participant.

Page [][][]

MTN 004 (136)

AE-1 (420)

Participant ID

[][][] - [][][][][] - []
Site Number Participant Number Chk

Adverse Experience Log

Date Reported to Site

[][] [][][] [][]
dd MMM yy

1. Adverse Experience (AE)

Record diagnosis if available. Include anatomical location, if applicable.

English (if above is in Local Language): _____

2. Onset Date

[][] [][][] [][]
dd MMM yy

3. Severity

- Grade 1 - Mild
- Grade 2 - Moderate
- Grade 3 - Severe
- Grade 4 - Life-threatening
- Grade 5 - Death

4. Relationship to Study Product

- Definitely related
- Probably related
- Possibly related
- Probably not related
- Not related

Record reason why AE is "not related" in Comments below.

5. Study Product Administration

- No change
- Held
- Permanently discontinued
- N/A

Change in Administration NOT APPLICABLE FOR THIS PROTOCOL

6. Status/Outcome

- Continuing
- Resolved
- Death
- Severity/frequency increased Report as new AE.
- Continuing at end of study participation

6a. Status/Outcome Date

Leave blank if Status/Outcome is "Continuing."

[][] [][][] [][]
dd MMM yy

7. Treatment Mark "None" or all that apply.

- None
- Medication(s) Report on Concomitant Medications Log.
- New/Prolonged hospitalization Comment below.
- Procedure/Surgery Comment below.
- Other Comment below.

8. Is this AE serious according to ICH guidelines?

yes no

9. Has/will this AE be reported as an EAE?

10. This AE was first reported at visit:

Visit code required (regular or interim).

[][] [][]

Comments: _____

English (if Comments above are in Local Language): _____

Adverse Experience Log (AE-1)

Purpose: To document any Adverse Experience (AE) reported by the participant or clinically observed as defined by the protocol.

General Information/Instructions: Do not record a condition as an AE if it existed at enrollment as a pre-existing condition, unless it increases in severity or frequency. If a cluster of symptoms reported on separate AE Log pages is later attributed to a single diagnosis, change the earliest reported symptom to the final diagnosis. In addition, mark the AE Log pages for the other symptoms with the words “Delete due to diagnosis on AE page #” (specify page number of diagnosis AE).

Item-specific instructions:

- **Page:** Number pages sequentially throughout the study, starting with 001. Do not repeat page numbers. Do not renumber any AE Log pages after faxing, unless instructed by SCHARP.
- **Item 1:** Whenever possible, provide a diagnosis instead of listing a cluster of symptoms. If no diagnosis is identified, each symptom must be recorded on a separate page of the AE Log. If an abnormal lab value is reported, record the lab assay with the direction (i.e., increased or decreased) of the abnormality. For example, “decreased hematocrit” or “increased ALT.”
- **Item 2:** At minimum, month and year are required. Record one of the following, as appropriate: the date on which the participant reports first experiencing the AE; if the AE is discovered during the study visit exam, record the date of the study visit exam; if the AE is an abnormal lab result, record the date on which the specimen was collected.
- **Item 3:** To grade the severity of an AE, consult the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences* and the Addendum 1 (*Female Genital Grading Table for Use in Microbicide Studies*.)
- **Item 4:** When judging causal association (relationship) between an AE and the study agent consult the terms used in DAIDS-sponsored studies as documented in the *Manual for Expedited Reporting of Adverse Events to DAIDS*.
 - **NOTE: IN CASES OF DEATH**, when relationship of study product is under investigation, write “Pending” in the adjacent white space until relationship has been determined. Update accordingly.
- **Item 5:**
 - **No change:** Mark if the AE does NOT result in a study product hold, permanent discontinuation, or change in administration.
 - **Held:** Mark if the AE results in a study product hold. If multiple AEs are reported at the same visit, mark “Held” for the AE(s) that contributed to the product hold.
 - **Permanently discontinued:** Mark if the AE results in permanent discontinuation of study product. If multiple AEs are reported at the same visit, mark “Permanently discontinued” for the AE(s) that contributed to the permanent discontinuation.
 - **N/A (not applicable):** Mark if the AE occurred after the participant had completed all administration of the study product, or the study product is held or permanently discontinued for a different AE or other reason, or the AE is Grade 5-death.
- **Item 6:**
 - **Continuing:** AE is continuing at the time it is reported.
 - **Resolved:** Condition is no longer present, or returned to the pre-enrollment severity/frequency. If a participant is taking a medication to control an AE that arose during study participation, it is not considered resolved.
 - **Death:** Mark only if the severity of this AE is Grade 5. Any other AEs continuing at the time of death should be changed to “continuing at end of study participation.”
 - **Severity/frequency increased:** If an AE increases in severity or frequency after it has been reported on the AE Log, line through the “Continuing” box previously marked and mark “Severity/frequency increased.” Record the date of increase in the “Status/Outcome Date.” Report the increase in severity or frequency as a new AE. For this new AE, the “Onset Date” will be the date that the severity or frequency increased. Note that decreases in severity should not be recorded as new AEs.
 - **Continuing at end of study participation:** Mark this box whenever an AE is continuing at the time of participant study termination.
- **Item 6a:** At minimum, month and year are required. Record one of the following, as appropriate: the date on which the participant no longer experienced the AE; or the date of the study visit or specimen collection at which the change in status/outcome is first noted.
- **Item 7:** Indicate if treatment was clinically indicated for the AE, regardless of whether the treatment was actually used. Also mark this item if the participant self-treated.
- **Items 8 and 9:** For questions about ICH guidelines and EAE reporting, refer to the *Manual for Expedited Reporting of Adverse Events to DAIDS*.

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MTN 004 (136)



PH-1 (410)

Visit Code .

Participant ID

- -
Site Number Participant Number Chk

Product Hold/Discontinuation

1. Date product hold was initiated:
dd MMM yy

2. Why is product being held?

pregnancy

STI/RTI requiring treatment

other adverse experience

AE Log page #(s)

other, specify: _____

3. Date of last study gel application:
dd MMM yy

4. Was the participant instructed to resume study gel use?

yes

*no
(permanently
discontinued)*

End of form.

*no
(hold continuing
for another reason)*

In item 4a, record the date on which study gel use would have been resumed if not being held for another reason.

4a. Date participant instructed to resume study gel use:

dd MMM yy

Visit Code .

Comments: _____

Product Hold/Discontinuation (PH-1)

This form is used to document temporary holds and permanent discontinuations of study gel. This form is completed each time a participant is instructed to temporarily stop (hold) or permanently discontinue study gel use prior to the Two-week Clinic Visit. If, at the same study visit, a product hold/discontinuation is initiated for more than one reason, complete a Product Hold/Discontinuation form for each reason. The same visit code should be used on each form.

In the case of temporary product holds, do not wait for information about product resumption to fax the form— fax this form to SCHARP DataFax as soon as items 1 through 3 have been completed. Refax the form once item 4 has been completed.

Item-specific Instructions:

- **Visit Code:** Record the visit code at which the participant was instructed by a study staff member to hold or permanently discontinue study gel use. If the product is being held or permanently discontinued as a result of an adverse experience, the Visit Code recorded on this form should match the visit code recorded in item 10 of the AE Log documenting the product hold/permanent discontinuation.
- **Item 1:** Record the date on which the participant was instructed to hold or permanently discontinue study gel use.
- **Item 2:** Mark the box to the left of the one reason which **best** describes why the participant is being instructed to hold or permanently discontinue gel use. Mark only one. If product is being held or discontinued due to an adverse experience, record the page number(s) of the AE Log documenting the product hold or permanent discontinuation. If the product hold/discontinuation is due to a reason other than the ones listed, mark “other, specify” and record the reason for the hold/discontinuation on the line provided.
- **Item 3:** Record the date the participant last applied study gel. Use a best estimate if the actual date cannot be determined.
- **Item 4:** Complete this item once study staff have determined that the participant can resume study gel use or have determined that she is permanently discontinued from study gel use. Mark this item “yes” if study staff instructed the participant that she can resume use of study gel. If the participant was permanently discontinued from study gel use, mark the “no (permanently discontinued)” box and end the form - leave item 4a blank. If the reason for the product hold, as recorded in item 2, has resolved but there is a concurrent reason (e.g., pregnancy) for continuing the product hold, mark “no (hold continuing for another reason).” In item 4a, record the date the participant would have been instructed (by site staff) to resume study gel use if it were not held for another reason.
- **Item 4a:** Record the date and visit code on which the participant was told by a study staff member that she could resume study gel use.

SAMPLE Do NOT FAX TO DATAFAX



Visit Code [][] . []

1

MTN 004 (136)

GBA-1 (281)

Participant ID

[][][] - [][][][][] - []
Site Number Participant Number Chk

Genital Bleeding Assessment

Visit Date

[][] [][][] [][]
dd MMM yy

This form should not be completed for pregnant participants. This form is completed whenever an episode of unexpected genital bleeding is self-reported by the participant and/or clinically observed with no identifiable source. Completion of this form is not required for episodes of expected genital bleeding.

- 1. First day of participant's last menstrual period: [][] [][][] [][] OR [] amenorrheic. Obtain from Follow-up Medical History form. If amenorrheic, go to item 4.
2. Last day of participant's last menstrual period: [][] [][][] [][] Obtain from Follow-up Medical History form.
3. Length in days of participant's last menstrual period (based on dates recorded in items 1 and 2): [][] days
4. First day of genital bleeding episode: [][] [][][] [][] Per participant report or clinical exam.
5. Last day of genital bleeding episode: [][] [][][] [][] OR [] ongoing
6. Total number of days of genital bleeding: [][] days OR [] ongoing
7. According to the participant, was the amount of genital blood a normal amount, lighter amount, or heavier amount when compared to the heaviest flow day of her regular menses? normal lighter heavier unknown N/A
8. According to the participant or the clinician, what color was the genital blood? bright red brown unknown
9. According to the participant, did she continue to use study gel during this genital bleeding episode? yes no N/A. If yes or N/A, go to item 11.

Genital Bleeding Assessment (GBA-1)

This form is completed by the study clinician, and used to guide study clinicians' assessment of genital bleeding events that occur during follow-up. This form is completed each time an episode of unexpected genital bleeding is self-reported by a study participant and is either not observed during pelvic examination, or is clinically-observed with no identifiable source. Specifically, this form guides clinicians to collect and consider information on the many factors that may contribute to the unexpected genital bleeding event. Study clinicians should review the Baseline Medical History form and refer to SSP Section 10 to determine whether or not an episode of genital bleeding is unexpected.

Item-specific Instructions:

- **Visit Code:** Record the visit code assigned to the visit. See Section 14.3.2 of the Study-Specific Procedures Manual for more specific information on assigning visit codes. Note that for regularly scheduled follow-up visits, the visit code is equal to the week on study plus 2.0. For example, the One-week Clinic Visit is assigned a visit code of "03.0," the Two-week Clinic Visit is assigned a visit code of "04.0," etc.
- **Item 1:** Mark "amenorrheic" if the participant has been without menses for at least the past three cycle intervals, or the past 6 months, whichever is shorter. If "amenorrheic" is marked, leave items 1–3 blank and go to item 4.
- **Item 5:** If the participant experienced intermittent bleeding as part of the same episode of genital bleeding, record the last date in which she experienced bleeding for that episode.
- **Item 6:** Record the total number of days in which the participant experienced bleeding during this genital bleeding episode. For example, if the participant experienced bleeding over 7 consecutive days and bled each of the 7 days, record "07." If the participant experienced genital bleeding over a 6-day period, but only bled on days 1, 2, 4, and 7, record "04."
- **Item 7:** Mark "unknown" in cases where the information is not known by the participant. Mark "N/A" if the genital bleeding was not reported by the participant, but was observed during the pelvic examination only.
- **Item 8:** Mark "unknown" in cases where the information is not known by the participant or the clinician.

SAMPLE: Do NOT FAX TO DATAFAX



Visit Code [][] . []

1

MTN 004 (136)

GBA-2 (282)

Participant ID

[][][] - [][][][][] - []
Site Number Participant Number Chk

Genital Bleeding Assessment

10. Number of days between last application of study gel and first day of genital bleeding episode: [][] days

11. According to the participant, did the genital bleeding occur within 2 days after...

- 11a. vaginal sex? [] yes [] no
- 11b. painful vaginal sex? [] yes [] no
- 11c. application of the study gel? [] yes [] no [] N/A
- 11d. painful or uncomfortable application of the study gel? [] yes [] no [] N/A
- 11e. painful or uncomfortable insertion or removal of any other vaginal product/preparation? [] yes [] no [] N/A
- 11f. a pelvic or colpo exam? [] yes [] no

If yes to any, record related details in Comments.

If yes, record date of last pelvic/colpo exam in Comments.

11g. condom use? [] yes [] no

12. Is the participant currently using injectable contraceptives? Review Concomitant Medications Log. [] yes [] no -> If no, go to item 13.

12a. When was her last injection? [][] dd [][][] MMM [][] yy

12b. When is/was her next injection due? [][] dd [][][] MMM [][] yy -> Go to item 14.

13. Is the participant currently using (non-injectable) hormonal contraceptives? Review Concomitant Medications Log. [] yes [] no -> If no, go to item 14.

13a. Has the participant missed one or more days of contraceptives in the week before the genital bleeding started? [] yes [] no -> If no, go to item 14.

Genital Bleeding Assessment (GBA-2)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on page 1 of this form for a given participant and visit.
- **Item 12:** If the participant reports currently using injectable contraceptives, make sure the injectable contraceptives are listed on the participant's Concomitant Medications Log.

SAMPLE *DO NOT FAX*
TO DATAFAX



Visit Code

MTN 004 (136)

GBA-3 (283)

Participant ID

- -
Site Number Participant Number Chk

Genital Bleeding Assessment

13b. Did the participant miss two or more days of contraceptives?
yes no
 If yes, go to item 14.

13c. **For participants using oral contraceptives only:**
Did the participant make up the missed dose of oral contraceptives?
yes no

14. Based on all information available, is this bleeding unexpected?
yes no
 If no, end of form. DO NOT complete AE Log.

14a. Is this unexpected bleeding menstrual or non-menstrual?

menstrual

↓
**Complete AE Log.
Report as "menorrhagia" or
"menometrorrhagia." Grade per
"menorrhagia" row of the
Female Genital Toxicity Table.**

non-menstrual

↓
**Complete AE Log.
Report as "metrorrhagia" or
"postcoital bleeding." Grade per
"metrorrhagia" or
"postcoital bleeding" row of the
Female Genital Toxicity Table.**

14b. Record Adverse Experience Log page:
AE Log Page #

Comments: _____

Genital Bleeding Assessment (GBA-3)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on page 1 of this form for a given participant and visit.
- **Item 13:** Non-injectable hormonal contraceptives include oral contraceptives (“the pill”), Ortho-Evra (“the patch”), and vaginal rings. If the participant reports currently using non-injectable hormonal contraceptives, make sure these are listed on the participant’s Concomitant Medications Log.
- **Item 13c:** This item applies only to those participants using oral contraceptives. For participants who do not use oral contraceptives, leave item 13c blank and go to item 14.
- **Item 14:** Review the Baseline Medical History form and refer to SSP Section 10 to determine whether or not the genital bleeding is unexpected. If the response is “yes” and the genital bleeding is determined to be unexpected, refer to protocol Appendix II for guidance on study gel administration.
- **Item 14a:** If the unexpected genital bleeding is:
 - **menstrual** - grade the AE of menorrhagia [defined as prolonged (more than 7 days) or excessive (>80 mL) uterine bleeding] or menometrorrhagia (defined as prolonged uterine bleeding occurring at irregular intervals) using the “menorrhagia” row of the *Female Genital Toxicity Table* (protocol Appendix IX).
NOTE: unexpected menstrual bleeding is defined as menstrual bleeding that is heavier in volume or longer in duration than the participant’s usual menses (as documented on the Baseline Medical History form). Refer to SSP Section 10 for further information.
 - **non-menstrual** - grade an AE of metrorrhagia (intermenstrual bleeding) using the “metrorrhagia” row of the *Female Genital Toxicity Table* (protocol Appendix IX). Grade an AE of postcoital bleeding using the “postcoital bleeding” row of the *Female Genital Toxicity Table*.
NOTE: unexpected non-menstrual genital bleeding—regardless of severity—that is associated with an observed pelvic exam finding should be reported as an AE, with the AE description = “bleeding source and location” (e.g., ulceration-vaginal). Unexpected non-menstrual bleeding—regardless of severity—that is associated with an underlying cause (e.g., fibroids, uterine laceration, trauma) should be reported as an AE, with the diagnosis as the AE description. Refer to SSP Section 10 for further information.
- **Item 14b:** Record the AE Log page number of the AE reported for this unexpected genital bleeding episode. When determining the relationship to study product, carefully review the information recorded in items 11–13c of this form. Record information relevant to the product relatedness determination in the Comments section of the AE Log.
- **Comments:** Record any necessary or additional information at the bottom of the form.

SAMPLE *DO NOT FAX*
TO DATAFAX

MTN 004 (136)



PR-1 (440)

Visit Code

1

Participant ID

- -
Site Number Participant Number Chk

Pregnancy Report and History

PREGNANCY REPORT

1. Date of last menstrual period: ^{dd} ^{MMM} ^{yy}
2. Estimated date of delivery: ^{dd} ^{MMM} ^{yy}

PREGNANCY HISTORY

3. Has the participant ever been pregnant before? ^{yes} ^{no} → **If no, end of form.**
3a. Is this the participant's first pregnancy since enrollment in this study? ^{yes} ^{no} → **If no, end of form.**

3b. Number of full term live births (≥ 37 weeks):

3c. Number of premature live births (< 37 weeks):

3d. Number of spontaneous fetal deaths and/or still births (≥ 20 weeks):

3e. Number of spontaneous abortions (< 20 weeks):

3f. Number of therapeutic/elective abortions:

3g. Number of ectopic pregnancies:

4. Does the participant have a history of pregnancy complications or fetal/infant congenital anomalies before study enrollment? ^{yes} ^{no} → **If yes, document in participant's records.**

Comments: _____

Pregnancy Report and History (PR-1)

This form is used to report the pregnancy of a study participant post enrollment through termination.

- **Visit Code:** Record the visit code of the visit at which the participant was determined to be pregnant.
- **Item 1:** Record the first day or best estimate of the participant's last menstrual period. Complete date required.

Item 2: Complete date required

SAMPLE. Do NOT FAX
TO DATAFAX



Visit Code

1

MTN 004 (136)

PO-1 (441)

Participant ID

- -
Site Number Participant Number Chk

Pregnancy Outcome

Outcome unknown at end of study. _____
Staff Initials/Date
▶ **End of form. Fax to SCHARP DataFax.**

1. How many pregnancy outcomes resulted from the reported pregnancy?

2. OUTCOME #1

dd MMM yy

2a. Outcome Date

2b. Specify Outcome: Mark only one.

- full term live birth (≥ 37 weeks)
 - premature live birth (< 37 weeks)
 - spontaneous fetal death and/or still birth (≥ 20 weeks)
 - spontaneous abortion (< 20 weeks)
 - ectopic pregnancy
 - therapeutic/elective abortion
- 2b1. Method: C-section vaginal
- Complete AE Log and EAE Reporting form.

2c. Were any fetal/infant congenital anomalies identified? yes no not assessed

If only one outcome, end of form.

3. OUTCOME #2

dd MMM yy

3a. Outcome Date

3b. Specify Outcome: Mark only one.

- full term live birth (≥ 37 weeks)
 - premature live birth (< 37 weeks)
 - spontaneous fetal death and/or still birth (≥ 20 weeks)
 - spontaneous abortion (< 20 weeks)
 - ectopic pregnancy
 - therapeutic/elective abortion
- 3b1. Method: C-section vaginal
- Complete AE Log and EAE Reporting form.

3c. Were any fetal/infant congenital anomalies identified? yes no not assessed

Comments: _____

26-MAR-07

0 1
Language

14-112
Staff Initials / Date

Pregnancy Outcome (PO-1)

This form is used to report the pregnancy outcome(s) of a pregnancy reported post enrollment through termination. A **Pregnancy Outcome** form is required for each **Pregnancy Report and History** form completed for a participant. This form is completed when information about a pregnancy outcome becomes available to study staff. If an outcome is unknown at study end, mark the “Outcome unknown at end of study” box at the top of the page and fax to DataFax. When the outcome is known, draw a line through this box, record the outcome, and refax. A pregnancy outcome can be an infant or a fetus. The conception of twins should result in reporting of two outcomes. If a pregnancy results in more than two outcomes, contact SCHARP for guidance on how to complete this form.

- **Visit Code:** Record the visit code of the participant’s corresponding **Pregnancy Report and History** form.
- **Specify Outcome:** If the outcome is therapeutic/elective abortion, note that while the abortion itself is not an Adverse Experience (AE), if the abortion is performed due to a pregnancy complication, the pregnancy complication should be reported on an **Adverse Experience Log**, with “procedure/surgery” marked under “Treatment.”

Congenital anomalies: This item should be updated if information becomes available during the mother’s (the study participant’s) study follow-up period regarding a congenital anomaly. If a woman on study has a baby with a congenital anomaly and the infant does not have his/her own participant ID, report the event as an AE and record in item 1 “Congenital Anomaly in Offspring.” Record the PTID of the woman on study (mother) on the form, just as you would for any other AE reported for the participant.

SAMPLE *DO NOT FAX*
TO DATAFAX

MTN 004 (136)



MV-1 (463)

Visit Code

. 0

1

Participant ID

- -

Site Number

Participant Number

Chk

Missed Visit

Form Completion Date

dd

MMM

yy

dd

MMM

yy

1. Target Visit Date:

2. Reason visit was missed. *Mark only one.*

- unable to contact participant
- unable to schedule appointment(s) within (allowable) window
- participant refused visit
- participant incarcerated
- participant institutionalized
- participant withdrew from the study —————> **Complete a Termination form.**
- participant deceased —————> **Complete a Termination form (Complete an Adverse Experience Log if applicable).**
- other, specify:

Comments: _____

Missed Visit (MV-1)

Purpose: Complete this form whenever an enrolled participant misses a required visit according to the visit window outlined in the protocol or Study Specific Procedures (SSP).

General Information/Instructions: If the QC Report indicates that a visit is overdue, confirm that the visit was missed before completing a Missed Visit form. Fax this form when it is determined that a visit has been missed and cannot be completed within the visit window. Record the Visit Code of the visit that was missed. Record the date that the form was completed. This will not necessarily be the date of the missed visit. A complete date is required.

Item-specific Instructions:

- **Item 1:** Record the target date of the visit. A complete date is required.
- **Item 2:** Record the reason the participant missed the visit.

SAMPLE. Do NOT FAX
TO DATAFAX

MTN 004 (136)



AA-1 (272)

Visit Code .

1

Participant ID

- -
Site Number Participant Number Chk

Acceptability Assessment

Visit Date

dd MMM yy

One goal of this research is to understand how acceptable study gel use is to women and their partners. I am now going to ask you some questions about your experiences using the study gel and how study gel use has affected your relationship(s) with sexual partners. Your honest answers will be very helpful to us.

1. If your study gel is found to protect people from getting HIV, how likely would you be to use it during vaginal intercourse?

Showcard #1 very likely likely unlikely very unlikely

2. What do you like about your study gel? DO NOT read response categories aloud. Mark all that apply.

- 2a. no response
- 2b. nothing
- 2c. may protect against HIV
- 2d. may protect against STIs
- 2e. can use without partner's knowledge
- 2f. easy to use
- 2g. method is under her control
- 2h. made sex more pleasurable
- 2i. did not interrupt sex
- 2j. appearance/smell
- 2k. other, specify: Local Language: _____

If only one response box is marked, English: _____ go to item 3 on page 2.

2l. Which of these do you like most? DO NOT read response categories aloud.

<input type="checkbox"/> no response	<input type="checkbox"/> method is under her control
<input type="checkbox"/> nothing	<input type="checkbox"/> made sex more pleasurable
<input type="checkbox"/> may protect against HIV	<input type="checkbox"/> did not interrupt sex
<input type="checkbox"/> may protect against STIs	<input type="checkbox"/> appearance/smell
<input type="checkbox"/> can use without partner's knowledge	<input type="checkbox"/> other, specify:
<input type="checkbox"/> easy to use	Local Language: _____
	English: _____

Acceptability Assessment (AA-1)

This form is used to collect study gel acceptability information from study participants. This is an interviewer-administered form, and it is administered only once to each enrolled participant at her Two-week Clinic Visit.

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **Item 2:** If the participant refuses or is unable to give a response to any item(s), mark the “no response” box.
- **Item 2:** Do not read any of the response categories aloud. Instead, read the question and mark the box(es) that correspond to each reported characteristic the participant likes about the study gel. If the participant gives a response that does not correspond to one of the listed categories, mark the “other, specify” box and record the participant’s verbatim (word-for-word) response. If “no response” or “nothing” is marked, no other response box should be marked. If only one response box is marked, leave item 21 blank and go to item 3.
- **Item 21:** Do not read any of the response categories aloud. Instead, read the question, and based on the participant’s responses to item 2, mark the box that corresponds to the one characteristic the participant likes most about the study gel. If she reports more than one, ask her to choose which of the characteristics she likes most. If the participant gives a response that does not correspond to one of the listed response categories, mark the “other, specify” box and record the participant’s verbatim (word-for-word) response.

SAMPLE. DO NOT FAX
TO DATAFAX

MTN 004 (136)

AA-2 (273) Visit Code

□□□.□□

1

Participant ID

□□□-□□□□□□-□
Site Number Participant Number Chk

Acceptability Assessment

3. What do you not like about your study gel? *DO NOT read response categories aloud. Mark all that apply.*

<input type="checkbox"/> 3a. no response	<input type="checkbox"/> 3g. remembering to use it
<input type="checkbox"/> 3b. nothing	<input type="checkbox"/> 3h. difficult to store and/or discard
<input type="checkbox"/> 3c. messy	<input type="checkbox"/> 3i. appearance/smell
<input type="checkbox"/> 3d. interrupted sex	<input type="checkbox"/> 3j. other, specify:
<input type="checkbox"/> 3e. made sex less pleasurable	<i>Local Language:</i>
<input type="checkbox"/> 3f. difficult to use, specify:	_____
<i>Local Language:</i>	<i>English:</i>
_____	_____
<i>English:</i>	

▶ *If only one response box is marked, end of form.*

3k. Which of these do you dislike most? *DO NOT read response categories aloud.*

no response

nothing

messy

interrupted sex

made sex less pleasurable

difficult to use

remembering to use it

difficult to store and/or discard

appearance/smell

other, specify:

Local Language: _____

English: _____

Acceptability Assessment (AA-2)

Item-specific Instructions:

- **Visit Code:** Make sure that the Visit Code recorded on this page matches the Visit Code recorded on all other pages of this form for a given participant and visit.
- **Item 3:** If the participant refuses or is unable to give a response to any item(s), mark the “no response” box.
- **Item 3: Do not** read any of the response categories aloud. Instead, read the question and mark the box(es) that correspond to each characteristic the participant does not like about the study gel. If the participant gives a response that does not correspond to one of the listed categories, mark the “other, specify” box and record the participant’s verbatim (word-for-word) response on the adjacent specify line(s). If the participant’s response is “difficult to use,” probe for more specific information as to why the study gel is difficult to use and record the participant’s verbatim (word-for-word) response on the adjacent specify line(s). If “no response” or “nothing” is marked, no other response box should be marked. If only one response box is marked, leave item 3k blank.
- **Item 3k: Do not** read any of the response categories aloud. Instead, read the question, and based on the participant’s responses to item 3, mark the box that corresponds to the one characteristic the participant dislikes most about the study gel. If she reports more than one, ask her to choose which of the characteristics she dislikes most. If the participant gives a response that does not correspond to one of the listed response categories, mark the “other, specify” box and record the participant’s verbatim (word-for-word) response.

If the participant refuses or is unable to give a response to any item(s), draw a line through the response boxes, write “don’t know” or “refused,” and initial and date the note in the white space next to the item.

SAMPLE. Do NOT FAX TO DATAFAX

MTN 004 (136)



IV-1 (350)

Visit Code

1

Participant ID

- -
Site Number Participant Number Chk

Interim Visit

Visit Date

dd MMM yy

1. What is the reason for this interim visit? *Mark all that apply.*

- 1a. in-person visit to report new symptoms → **Complete Adverse Experience Log.**
- 1b. phone call from participant to report new symptoms → **Complete Adverse Experience Log.**
- 1c. follow-up of an AE → **Update Adverse Experience Log if indicated.**
- 1d. participant needs study gel
- 1e. participant is returning study gel
- 1f. other, specify: _____

2. hCG for pregnancy: *not done* *negative* *positive* → **If positive, complete Pregnancy Report and History form and Product Hold/Discontinuation form.**

2a. Specify reason(s): ← _____

3. Besides this form, what other DataFax study forms (with the same visit code as this form) were completed for this visit? *Mark "none" or all that apply.*

- 3a. none
- 3b. Follow-up Pelvic Exam
- 3c. Pelvic Laboratory Results
- 3d. STI Laboratory Results
- 3e. Adverse Experience Log (new)
- 3f. Product Hold/Discontinuation
- 3g. Safety Laboratory Results
- 3h. Follow-up Genital Symptoms
- 3i. Genital Bleeding Assessment
- 3j. other, specify: _____

→ 3e1. How many **new** AE Log pages were completed for this visit? # of pages

4. At this visit, how many **unused** applicators did the participant return? # of **unused** applicators returned

5. ~~At this visit, how many **unused** applicators did the participant return? # of **unused** applicators returned~~
NO LONGER APPLICABLE FOR THIS PROTOCOL.

6. At this visit, how many cartons of study gel were dispensed to the participant? # of cartons dispensed

6a. Randomization code of first dispensed carton:

6b. Randomization code of second dispensed carton: OR N/A

→ **If 0, end of form.**

Comments: _____

Interim Visit (IV-1)

The Interim Visit form is used to document interim visits that occur during study follow-up. Any other forms completed for this visit must have the same Visit Code as the corresponding Interim Visit form.

This form is used to document interim visits during follow-up. See Section 14.3.2 of the Study-Specific Procedures Manual for a definition and examples of interim visits that require an Interim Visit form to be completed. Note that all DataFax forms completed for an Interim Visit must have the same interim Visit Code as the Interim Visit form.

Item-specific Instructions:

- **Visit Code:** The following guidelines should be used for assigning the interim visit code:
 - Record the two-digit whole number visit code for the most recent scheduled regular visit. For example, if the most recent scheduled regular visit was Week 4 (Visit Code = 03.0), record “03” to the left of the decimal point in the visit code field.
 - Record the number that corresponds to the Interim Visit in the third box (the box to the right of the decimal point):
XX.1 = First Interim Visit after the most recent scheduled regular visit.
XX.2 = Second Interim Visit after the most recent scheduled regular visit.
- **Item 1:** Mark the box to the left of each reason(s) this Interim Visit was conducted. Mark all that apply.
- **Item 2:** A urine pregnancy test is required at each interim visit. Record the hCG urine pregnancy test result. If a required urine pregnancy test result is not available (specimen not collected and/or test not done), mark the “not done” box and complete item 2a.
*Note: A **Pregnancy Report and History** form must be completed for each pregnancy. Once a participant tests positive for hCG urine pregnancy and a **Pregnancy Report and History** form (PR-1) has been completed for this pregnancy, subsequent positive pregnancy test results should not be recorded on a new PR-1 (unless they represent a new pregnancy).*
- **Item 3:** For each DataFax form completed for this visit, mark the box to the left of the form name. Mark all boxes that apply. Note that marking a box indicates that a DataFax form with the same visit code as this form will be faxed to SCHARP DataFax.
 - **none:** Mark this box if the Interim Visit form is the **only** DataFax form completed for this visit.
 - **Adverse Experience Log (new):** Mark this box if a new (previously unreported) AE is reported or observed at this visit. If the box to the left of “Adverse Experience Log (new)” is marked, record in item 3a how many **new** AE Log pages were completed for this visit. For example, if two new AEs were reported, record “02.” Note that the Visit Code recorded in item 10 of these two AE Log pages should be the same as the Visit Code recorded on this form.
 - **other, specify:** Mark this box if a DataFax form(s) other than the ones listed was completed for this visit. Specify the form name(s) on the line provided.
- **Item 4:** Record the number of **unused** study gel applicators the participant returned at this visit only.
- **Item 6:** Record the number of cartons of study gel given to the participant at this visit. This will be the same amount documented on the **Study Gel Request Slip** (and/or on the **Replacement Prescription**, if replacement carton(s) are also dispensed), unless documentation from the pharmacy staff states otherwise.
- **Item 6a:** From the site pharmacist (or designee), obtain and record the unique 3-digit randomization code present on the carton label of the first carton of study gel dispensed to the participant at this visit.
- **Item 6b:** From the site pharmacist (or designee), obtain and record the unique 3-digit randomization code present on the carton label of the second carton of study gel dispensed to the participant at this visit. If a second carton was not dispensed at this visit, mark the “N/A” box.

SAMPLE *DO NOT FAX*
TO DATAFAX

MTN 004 (136)



CT-1 (485)

Participant ID

			-						-		
Site Number				Participant Number							Chk

CASI Tracking

Form Completion Date

<i>dd</i>		<i>MMM</i>			<i>yy</i>

- | | | | | | | | | | | |
|----|---|--------------------------|--------------------------|--|--|--|--|--|--|--|
| | | <i>completed</i> | <i>not completed</i> | | | | | | | |
| 1. | Baseline Behavioral Questionnaire | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | |
| | | <i>not required</i> | <i>completed</i> | <i>not completed</i> | | | | | | |
| 2. | Acceptability and Adherence Questionnaire | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | |
| | | | | <i>visit code</i> | | | | | | |
| | | | | <table border="1" style="display: inline-table; width: 40px; height: 20px;"> <tr><td style="width: 20px;"></td><td style="width: 20px;"></td></tr> </table> <table border="1" style="display: inline-table; width: 40px; height: 20px;"> <tr><td style="width: 20px;"></td><td style="width: 20px;"></td></tr> </table> . <table border="1" style="display: inline-table; width: 40px; height: 20px;"> <tr><td style="width: 20px;"></td><td style="width: 20px;"></td></tr> </table> | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | <i>not required</i> | <i>completed</i> | <i>not completed</i> | | | | | | |
| 3. | Study Burden Questionnaire | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | |
| | | | | <i>visit code</i> | | | | | | |
| | | | | <table border="1" style="display: inline-table; width: 40px; height: 20px;"> <tr><td style="width: 20px;"></td><td style="width: 20px;"></td></tr> </table> <table border="1" style="display: inline-table; width: 40px; height: 20px;"> <tr><td style="width: 20px;"></td><td style="width: 20px;"></td></tr> </table> . <table border="1" style="display: inline-table; width: 40px; height: 20px;"> <tr><td style="width: 20px;"></td><td style="width: 20px;"></td></tr> </table> | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

Comments: _____

CASI Tracking (CT-1)

Purpose: This form is used to document participant completion of the Computer-Assisted Self-Interview (CASI) web-based questionnaires during the study.

General Information/Instructions: This form is completed once for each enrolled participant at the scheduled exit/end of study visit, or when it is determined that the participant is no longer participating in the study.

Item-specific instructions:

- **Item 1:** Mark the “completed” box if the participant completed all or only a portion of the Baseline Behavioral Questionnaire. Mark the “not completed” box if the participant did not complete any part of the questionnaire.
- **Item 2:** Mark the “not required” box if the participant terminated the study prior to her 2-Week Clinic Visit and did not complete the questionnaire. Mark the “completed” box if the participant completed all or only a portion of the Acceptability and Adherence Questionnaire. Record the Visit Code of the visit when the participant completed the questionnaire. Mark the “not completed” box if the participant completed her 2-Week Clinic Visit and/or her 3-Week Clinic Visit, but did not complete any part of the questionnaire.
- **Item 3:** Mark the “not required” box if the participant terminated the study prior to her 3-Week Clinic Visit and did not complete the questionnaire. Mark the “completed” box if the participant completed all or only a portion of the Study Burden Questionnaire. Record the Visit Code of the visit when the participant completed the questionnaire. Mark the “not completed” box if the participant completed her 3-Week Clinic Visit, but did not complete any part of the questionnaire.

SAMPLE. Do NOT FAX
TO DATAFAX



MTN 004 (136)

ESI-1 (489)

Participant ID

<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	
Site Number				Participant Number						Chk	

End of Study Inventory

Form Completion Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<i>dd</i>		<i>MMM</i>			<i>yy</i>		

1. What is the **highest** visit code (scheduled or interim) for this participant, recorded on a form submitted via DataFax?.....

visit code

<input type="text"/>	<input type="text"/>	.	<input type="text"/>
----------------------	----------------------	---	----------------------

2. How many interim visits were conducted for this participant during the study and recorded on a form submitted via DataFax?.....

of interim visits

<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------

3. Indicate the **highest** page number submitted for this participant for each of the following forms:

3a. Adverse Experience Log (AE-1) *page #* **OR** *no pages submitted*

3b. Concomitant Medications Log (CM-1) *page #*

3c. Pre-existing Conditions (PRE-1) *page #* **OR** *no pages submitted*

Comments: _____

End of Study Inventory (ESI-1)

This form is used to confirm that SCHARP has received all study data for a given participant. Complete this form once for each enrolled participant after participant has terminated from the study (as documented by a Termination form).

- **Form Completion Date:** Complete date required.
- **Item 1:** Record the highest visit code (last visit for which DataFax forms were submitted). If the participant's last visit was missed (as documented by a Missed Visit form), record the visit code of the missed visit.
- **Item 2:** Record the total number of Interim Visit DataFax forms submitted for this participant. If no Interim Visit forms were submitted for the participant, record "000" in the boxes.
- **Item 3a:** Record the highest page number of the Adverse Experience Log submitted for this participant, even if that page was marked for deletion.
- **Item 3b:** Record the highest page number of the Concomitant Medications Log submitted for this participant.
- **Item 3c:** Record the highest page number of the Pre-existing Conditions form submitted for this participant.

SAMPLE: Do NOT FAX TO DATAFAX



MTN 004 (136)

TM-1 (490)

Participant ID

Site Number - Participant Number - Chk

Termination

1. Termination Date: dd MMM yy Date the site determined that the participant was no longer in the study.

2. Reason for termination. Mark only one.

2a. scheduled exit visit/end of study -> End of form.

2b. death, indicate date and cause if known

2b1. date of death dd MMM yy OR date unknown
2b2. cause of death OR cause unknown

Complete or update Adverse Experience Log.

- 2c. participant refused further participation, specify:
2d. participant unable to adhere to visit schedule
2e. participant relocated, no follow-up planned
2f. investigator decision, specify:
2g. unable to contact participant
2h. NOT APPLICABLE FOR THIS PROTOCOL.
2i. inappropriate enrollment
2j. invalid ID due to duplicate screening/enrollment
2k. other, specify:
2l. early study closure
2m. participant unable to adhere to study requirements

3. Was termination associated with...

3a. Adverse Experience? yes no don't know Record Adverse Experience Log page: page #

Comments:

Termination (TM-1)

The Termination form is completed for every enrolled participant at either the scheduled exit/end of study visit or when the participant is no longer participating in the study. A complete date is required, unless termination is due to death.

- **Item 2:** Although more than one of the listed reasons may describe why a participant left the study early, mark only the primary reason for termination.
 - **Item 2a:** Scheduled exit visit/end of study: Only mark 2a if the participant completes the protocol-defined final visit.
 - **Item 2b1:** At a minimum, the month and year are required.
 - **Item 2l:** Early study closure: Only mark 2l when instructed by SCHARP.

Item 3a: Record the page number of the Adverse Experience Log on which the AE was recorded. In situations where more than one AE is associated with termination, record the AE that most strongly influenced the decision to terminate.

Section 15 – Data Communiqués

For MTN 004, SCHARP will use “Data Communiqués” to document and communicate data decisions and procedures that are made or revised during the study. By using Data Communiqués, SCHARP avoids having to re-distribute a revised version of the Data Collection section of this SSP every time a form completion clarification or revision is made.

Data Communiqués are considered official study documentation. As such, each time a Data Communiqué is sent (via email), please circulate it among relevant staff for their review, print the Data Communiqué, and place it in this section of each MTN 004 SSP binder in your possession. Consider each Data Communiqué an official part of the SSP.

Each Data Communiqué sent will consist of three sections: a Reminders section, used to remind sites of specific data collection or forms completion procedures; a Clarification section, used to clarify data collection or form completion procedures; and an Updates section, used to communicate when an updated version of a form is being issued or to notify the sites that an updated version of the forms instructions is about to be distributed (for example).

Note that a “Data Communiqué” does not request specific actions or corrections to a particular participant’s data - it is just a listing of general items to keep in mind when performing data collection for the study.

MTN 004 Data Communiqué #1

July 31, 2008

This is official study documentation for MTN 004. Please circulate it among relevant staff for their review, print it, and place it in your MTN 004 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 004 SSP manual.

UPDATES

1. New SCHARP Project Manager

Corey Kelly has joined MTN 004 as the study's SCHARP Project Manager. Please copy both Karen Patterson (karenp@scharp.org) and Corey Kelly (ckelly@scharp.org) on all correspondences to SCHARP (until otherwise notified) in order to ensure a smooth transition.

2. Revised CRFs – Version 2.0, Dated 23-JUL-08

To account for changes present in protocol version 3.0, the following CRFs were updated as follows:

a. Follow-up Visit form

Item 4 (# of used applicators returned) was grayed out, since used applicators are no longer collected. The item 4 form instructions were deleted.

b. Interim Visit form

Item 5 (# of used applicators returned) was grayed out, since used applicators are no longer collected. The item 5 form instructions were deleted.

c. Follow-up Pelvic Exam form

- i. The colposcopy questions were renumbered as items 9 and 9a so that they now appear *after* the series of questions that ask about non-colposcopic findings which may lead to product holds/discontinuations.
- ii. The previous item 4 (“Do any of these exam findings involve vaginitis?”) was removed, since “vaginitis” was changed to “abnormal vaginal discharge” in protocol Appendix II. The form instructions for this item were also deleted. (Abnormal vaginal discharge is already captured in item 1a).
- iii. The word “(ulceration)” was added to the questions numbered as items 3 and 3a in the new version of the form.
- iv. The word “suggest” was replaced with “involve presumed” and appears before the word “cervicitis” for item 4 in the new version of the form.
- v. The note off the new item 9 “If finding is new, complete Adverse Experience Log as applicable” was removed.
- vi. Form instructions were added for items 1a2, 1a8, 1a16, and 2-8.

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- vii. Item 7 text “intermenstrual bleeding” was replaced with “unexpected genital bleeding”, and the text “(that is not associated with an abnormal exam finding)” was added for further clarity.
 - viii. The instructions off the “yes” box for item 7 now refer to the Genital Bleeding Assessment form instead of the AE Log form.
 - ix. The follow-up question “Was the bleeding/spotting observed with no identifiable source?” was deleted.
- d. Adverse Experience Log
- The form instructions only changed to match the current standard MTN AE Log form instructions at SCHARP. These include reference to the DAIDS Female Genital Toxicity Table.
- e. Screening 1 Visit Eligibility (non-DataFax) form
- Items 22 and 23 were reworded to match the rewording of these eligibility criteria in protocol version 3.0.
- f. Screening 2 Visit/Enrollment Eligibility (non-DataFax) form
- Item 8 was reworded to match the rewording of this eligibility criterion in protocol version 3.0.
- g. Screening Summary (non-DataFax) form
- Items 2k and 2af were reworded to match the rewording of these eligibility criteria in protocol version 3.0.

These updated revised forms are version 2.0 and dated 23-JUL-08. All unused, previous versions of these forms (version 1.0, dated 26-MAR-07) must be destroyed.

3. CASI Tracking form

A new form, the CASI Tracking form, was added to the MTN 004 CRFs. The CASI Tracking form (version 1.0, dated 31-JUL-08) is a DataFax form and is used to capture completion of the web-based CASI questionnaires. One CASI Tracking form must be completed for each enrolled participant at her study exit visit.

The SCHARP Project Manager will contact each site to request that a CASI Tracking form be completed for each of the seven participants who enrolled in the study prior to the study pause.

CLARIFICATIONS

1. Pre-Existing Conditions form

Record on the Pre-Existing Conditions form *only* those conditions that are ongoing at the time of the participant’s Enrollment Visit. This includes chronic conditions, such as asthma and pre-menstrual symptoms.

REMINDERS

None

MTN 004 Data Communiqué #2

November 12, 2008

This is official study documentation for MTN 004. Please circulate it among relevant staff for their review, print it, and place it in your MTN 004 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 004 SSP manual.

UPDATES

1. Enrollment case report form (ENR-1)

A revised Enrollment CRF was distributed to both sites via email on 28-Oct-08. This revised form, dated 28-Oct-08, had a revision made to item 2a (the number of boxes for envelope number has been updated to 3 boxes). The previous version of the form should be removed and not used for any participants enrolling on or after October 28, 2008.

2. Recall and Re-issue of randomization envelopes

Due to an error identified in the Tampa randomization envelopes (a separate Memo to File has been provided to the site to document these events), all un-assigned MTN 004 Clinic and Replacement randomization envelopes provided to both sites in September, 2008 were recalled by SCHARP. These envelopes were reassembled at SCHARP, and re-issued to the sites during the first week of November, 2008. For the Tampa site, Clinic envelopes numbered 104-133 were re-issued, as were Replacement envelopes numbered 101-R and 102-127. For the San Juan site, Clinic envelopes numbered 134-166 and Replacement envelopes numbered 134-160 were re-issued. All of the re-issued envelopes are stamped with the date of "Nov 04 2008".

CLARIFICATIONS

1. Safety Laboratory Results (SL-1) form, item 2

For items 2a and 2b of the SL-1 CRF (neutrophils and lymphocytes), please record **both the percentage and absolute count results** for these items. For items 2c-2h, only a percentage **or** absolute count is needed. Please go back and record the absolute count for items 2a and 2b for all participants previously enrolled in the study (enrolled in 2007).

REMINDERS

1. Faxing of the CASI Tracking (CT-1) CRF

Note that the CASI Tracking CRF should be submitted to SCHARP once the participant has completed her participation in the study (along with the End of Study Inventory and Termination CRFs). Please do not fax this form to SCHARP until this time.



MTN 004 Data Communiqué #3

July 28, 2009

This is official study documentation for MTN 004. Please circulate it among relevant staff for their review, print it, and place it in your MTN 004 SSP Manual in the Data Communiqués section. This document is considered part of the MTN 004 SSP manual.

UPDATES

None.

CLARIFICATIONS

1. Enrollment CRF and participants who do not provide consent for long-term specimen storage and future testing

For enrolled MTN 004 participants who **do not** consent to long-term specimen storage and future testing, please document this by adding a note in the “Comments” section of the Enrollment (ENR-1) CRF. For enrolled participants who do provide this consent, no additional documentation is needed on the CRF.

Once the study is completed and all specimens have been analyzed, SCHARP will provide each site with a listing of those participants who did not consent to long-term storage. Instructions will also be provided for destroying any remaining stored specimens from the listed participants.

2. Study Gel Adherence CRF (SGA-1) completion for participants who have a product hold and/or permanent product discontinuation

Items 2 and 2a of the SGA-1 form should be completed based on the actual number of days the participant reports using study product less than 2 times per day, even if the participant did not use product because she was on a product hold or had permanently discontinued study product. If the participant was on product hold or permanent discontinuation and this is the reason she did not use product twice/day, please indicate this in the “Comments” section by adding a note like “participant on [product hold or permanently discontinued] since dd/MMM/yy”.

REMINDERS

None.

Section 16 - Study Reporting Plan

MTN 004 Statistical and Data Management Center (SDMC) Staff

Protocol Statistician:	Barbra Richardson
Project Manager:	Missy Cianciola
Statistical Research Associate:	Marla Husnik
Protocol Programmer:	Katie Weaver
CASI Programmer:	Lynda McVarish
Reporting Programmer:	Jim Sundberg
Data Coordinator:	Jennifer Schille
Document Specialist:	Lori Filipic
Laboratory Programmer:	Laura Robins-Morris
Clinical Affairs Safety Associate:	Yevgeny Grigoriev

16.1 Purpose of Reporting Plan

The purpose of this reporting plan is to describe the reports that the MTN SDMC (SCHARP) plans to generate for MTN 004.

The specific purposes of this plan are:

- To identify the purpose and content of each report;
- To identify those responsible for the preparation and distribution of each report;
- To identify who should review the reports so that corrective action (if necessary) is taken; and
- To ensure the Protocol Team approves the plan prior to study initiation.

This reporting plan was prepared by the MTN 004 SDMC Project Manager in collaboration with other MTN 004 SDMC staff.

16.2 Study Reports

Table 16-1 lists the reports the SDMC will produce and distribute via email. Table 16-2 lists the reports the SDMC will produce and make available via the Atlas website:

<http://atlas.ssharp.org>

Following the tables is a description of each report that includes the purpose of the report, who will prepare the report, and specific components of the report.

Table 16-1: MTN 004 SDMC Reports Distributed via Email

Report Title	Distribution Frequency	Email Distribution List
Data Quality Control (QC)	Every two weeks, or as needed	<ul style="list-style-type: none"> • Site Study Coordinators • Site Data Managers • CORE Clinical Research Managers • SDMC Project Manager
Clinical Data Quality Control (CQC) Queries	Weekly, or as needed	<ul style="list-style-type: none"> • Site Study Coordinators • Site Data Managers • CORE Clinical Research Managers • SDMC Project Manager
Study Monitoring Committee (SMC)	As determined by the SMC	<ul style="list-style-type: none"> • MTN 004 SMC members and observers • MTN 004 Protocol Chair • MTN 004 Site Investigators
Site Specimen Monitoring Report	Monthly	<ul style="list-style-type: none"> • Site Study Coordinators • Network Lab Representative • SDMC Project Manager
Summary Specimen Monitoring Report	Monthly	<ul style="list-style-type: none"> • Network Lab Representative • SDMC Project Manager

Table 16-2: MTN 004 SDMC Reports Posted on Atlas

Report Title	Update Frequency	Atlas Viewing Area
Enrollment and Retention	Every Week	Unsecure
Visit Adherence and Procedure Completion	Every 2 Weeks	Unsecure
Site Data Management Quality	Monthly	Unsecure
Safety Report	As determined by the MTN-004 Protocol Safety Review Team (PSRT)	Secure
Network Lab Assay Results Report	Monthly	Unsecure

16.2.1 Data Quality Control (QC) Report

Purpose: To identify and help correct missing and inconsistent data

Prepared and Distributed by: SDMC Data Coordinator

Components: Quality control notes; overdue visit reminders, missing page reminders

16.2.2 Clinical Data Quality Control (CQC) Queries

Purpose: To identify and help correct inconsistencies/questions identified in safety or clinical data

Prepared and Distributed by: SDMC Clinical Affairs Safety Associate

Components: Queries containing clinically-based questions about safety and clinical data.

16.2.3 Study Monitoring Committee Report

Purpose: To monitor study progress at each site

Prepared and Distributed by: Prepared by SDMC MTN 004 staff and distributed by SDMC Project Manager

Components: Summary by site and for the study overall of study design and history, accrual, retention, demographics, visit adherence. Site data management quality, and other components as requested by the SMC.

16.2.4 Site Specimen Monitoring Report

Purpose: To monitor storage in LDMS of those specimens marked as “stored” on study CRFs

Prepared by: SDMC Laboratory Programmer

Components: Site-specific listing of all discrepancies between the CRF stored specimen data and LDMS data.

16.2.5 Summary Specimen Monitoring Report

Purpose: To monitor storage in LDMS of those specimens marked as “stored” on study CRFs across all sites

Prepared by: SDMC Laboratory Programmer

Components: Summary listing for all sites of all discrepancies between the CRF stored specimen data and LDMS data.

16.2.6 Enrollment and Retention Report

Purpose: To monitor participant accrual and retention as reflected by data submitted to the SDMC (via DataFax)

Prepared by: SDMC Protocol Programmer

Components: Enrollment, includes the number of women enrolled each week and cumulatively. Retention, by visit. Includes: total enrolled (broken down by active, inappropriately enrolled, and lost to follow-up); number expected for a given visit; number not expected for a given visit; and total retention by visit calculated as the number of participants who have completed a visit divided by the total number of participants expected for the visit.

16.2.7 Visit Adherence and Procedure Completion Report

Purpose: To summarize site performance regarding study endpoint data collection

Prepared by: SDMC Statistical Research Associate

Components: Distribution of visits, including the number of days between target and actual visit dates, and the number of days between sequential follow-up visits. Listing of number and % of required PK blood specimens collected, genital specimens collected, safety lab tests completed, pelvic exams completed, pregnancy tests completed, and CASI questionnaire completion.

16.2.8 Site Data Management Quality Report

Purpose: To summarize site performance regarding data management and quality.

Prepared by: SDMC Project Manager

Components: Total number of CRF pages faxed to SCHARP, total number of QCs applied, % of QCs resolved, QC rate per 100 CRF pages, and mean days to fax in CRF pages. Reported cumulatively and for the previous month.

16.2.9 Safety Report

Purpose: To help the Protocol Safety Review Team monitor study participant safety as reflected by adverse experiences reported to the SDMC (via DataFax).

Prepared by: SDMC Reporting Programmer and SDMC Clinical Affairs Safety Associate

Components: Cumulative AE data reported to SCHARP via DataFax.

16.2.10 Network Lab Assay Results Report

Purpose: To monitor the receipt of lab assay results from the Network Lab.

Prepared by: SDMC Laboratory Programmer

Components: For each specimen analyzed by a Network Lab, the number of results expected (per CRF data) along with the number and percentage of results received and processed at SCHARP.