MTN-007 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	2.0	20 August 2010	• No Changes
2	Protocol	2.0	20 August 2010	• No Changes
3	Documentation Requirements	2.1	13 September 2010	• Updated to include new case report form (Enrollment Visit Eligibility)
4	Participant Accrual	2.1	17 December 2010	• Updated Section 4.2.4 to clarify participants may be rescreened if otherwise eligible but the 36 day screening and enrollment timeframe has passed due to unforeseen circumstances
5	Informed Consent	2.0	20 August 2010	• No Changes
6	Participant Follow-Up	2.1	17 December 2010	• Updated Section 6.10.3 to clarify study product completion procedures for participants randomized to receive gel
7	Visit Checklists	2.2	07 March 2011	• Updated the Screening, Enrollment, Treatment 1 and Treatment 2 Visits checklists to clarify that contraceptive counseling is applicable to all study participants; not only females of child bearing potential
8	Participant Retention	2.0	20 August 2010	• No Changes
9	Study Product Considerations for Non-Pharmacy Staff	2.1	07 January 2011	• Updated Section 9.6 to clarify allowable timeframe in which study product should be retrieved from a study participant following the Final Clinic Visit
10	Clinical Considerations	2.2	01 November 2010	• Updated Section 10.3 to clarify the Pre-existing Conditions CRF is to be completed at the Screening Visit and reviewed/updated at the Enrollment Visit
11	AE Reporting and Safety Monitoring	2.2	07 January 2011	• Updated Section 11.11.2 to include the Protocol Co-Chair as a member of the PSRT • Updated Section Appendices I and II to correct hyperlinks to the DAIDS Grading Tables • Updated Section Appendix III to include the revised PSRT Query Form • Updated Section 11.11.4 to update instructions for viewing and discussing PSRT queries via the PSRT Query Message Board on SCHARP/ATLAS
12	Laboratory Considerations	2.3	15 November 2010	• Updated Section 12.7.5 to revise processing procedures for the lavage for Epithelial Sloughing
13	Data Collection	2.1	13 September 2010	• Updated to include revised DataFax case report forms (AE Log and Pregnancy Outcome); revised (non-DataFax) case report forms (Medical Eligibility and Screening Visit Eligibility); and a new (non-DataFax) case report form (Enrollment Visit Eligibility)

14	Data Communiqués	2.0	20 August 2010	• Includes Data Communiqué #1 dated 03 September 2010; Data Communiqué #2 dated 13 September 2010; Data Communiqué #3 dated 23 September 2010 and Data Communiqué #4 dated 10 November 2010
15	Study Reporting Plan	2.0	20 August 2010	• No Changes
16	Behavioral Measures: Web-Based Questionnaires and Phone Reporting System	2.1	03 December 2010	• Section 6.2.2 was updated to clarify that participants must report any medical problems they are having to site staff rather than using the PRS to submit such concerns. • Updated to include new Section 16.2.3 which describes how to determine compensation owed to participants for calling into the PRS (prior to Final Clinic Visit). • Updated to include new Section 16.4 to clarify procedures for completing behavioral measures for participants who have permanently discontinued study product use.

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Section 10. Clinical Considerations

Section 11. Adverse Event Reporting and Safety Monitoring

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Section 1. Introduction

This section specifies the sources of procedural information available to MTN-007 study staff, the responsibilities of MTN-007 Investigators of Record (IoRs), and the process by which each study site is approved to begin implementation of MTN-007. Also included is information on required submissions to Institutional Review Boards.

1.1 Sources of Procedural Information

All study procedures must be conducted in accordance with the MTN-007 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.

Any study implementation questions that arise should be managed as follows:

- Study staff should contact the MTN CORE (FHI) Clinical Research Manager with all questions related to interpretation and proper implementation of the protocol.
- Questions related to data collection and management should be directed to the MTN CORE Statistical and Data Management Center (SDMC) Project Manager.
- Questions related to the collection, processing, testing, storage, and/or shipment of laboratory specimens should be directed to the MTN Network Laboratory (NL) Representative.
- Questions related to the investigational study products should be directed to the MTN CORE Pharmacist.
- Questions related to the administration of behavioral measures (Baseline Behavioral Questionnaire, the Adherence Questionnaire, and the Product Acceptability Questionnaire) should be directed to mtn007webtrouble@mtnstopshiv.org.

When in doubt as to whether questions pertain to protocol interpretation, data collection or laboratory procedures, contact the MTN-007 Management Team:

mtn007mgmt@mtnstopshiv.org

Site-specific contacts for the MTN CORE, SDMC, NL and study product are listed below.

FHI Clinical Research Manager:	Philip Andrew pandrew@fhi.org tel: 919.544.7040 extension 11213
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Contact information for all other MTN-007 protocol team members can be found in the protocol document or in the MTN directory at http://www.mtnstopshiv.org.

1.2 Investigator Responsibilities

MTN-007 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/node/187

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://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/ClinicalSite.aspx
http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/Regulatory.aspx

At each site, MTN-007 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-007 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-007 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-007 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-007 from all responsible regulatory authorities and IRBs. Each site also must complete Protocol Registration procedures with the DAIDS Regulatory Support Center (RSC) and study activation procedures with DAIDS and the MTN CORE (FHI), SDMC and NL prior to participant screening procedures. MTN CORE (FHI), SDMC, and NL will assist the sites with pre-implementation activities required for activation. On a site-by-site basis, the MTN CORE (FHI) will issue a Site-Specific Study Activation Notice 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. For additional information, refer to the protocol registration documents located at http://rsc.tech-res.com/protocolregistration/. For questions regarding protocol registration, please email

protocol@tech-res.com, fax 1-800-418-3544 or 1-301-897-1701, or phone 1-301-897-1707. Protocol registration must occur as a condition for site-specific study activation. Detailed information on the requirements of these pre-implementation steps is also located in the MTN MOP.

1.4 IRB/EC Submissions

Figures 1-1 and 1-2 list IRB submission and approval requirements pertinent to MTN-007. 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; however IRB 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; in such cases, all required documents must be submitted to and approved by the IRBs. If your IRB 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, and to request that the IRBs note the effective and expiry dates of all approvals. Submissions to your IRB should detail what documents are being forwarded for review. Similarly, replies from your IRB should list the documents that were reviewed and disposition for each document. Procedures for IRB communication must be documented in site-specific SOPs. Documentation of all correspondence to and from all responsible IRBs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in your site Essential Document files.

Figure 1-1
IRB Submissions Required Prior to Initiation of MTN-007

Document	Written Approval Required*
MTN-007 Protocol, Version 2.0	Yes
Informed consent forms: -Screening -Enrollment -Storage and Future Testing of Specimens *Note: MTN informed consent forms typically contain information on participant incentive amounts and schedule; however, incentives may be approved through submission of separate materials.*	Yes
Investigator of Record current CV	No
Investigator's Brochures for Tenofovir gel and HEC placebo gel and the Package Insert for Nonoxynol-9	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	If required by IRB/EC

*Denotes approvals required by US regulations and GCP guidelines.

Figure 1-2
IRB Submissions Required During and Following Conduct of MTN-007

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) *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.*	Yes
Investigator's Brochures for Tenofovir gel and HEC placebo gel and the Package Insert for Nonoxynol-9	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 CONRAD and the DAIDS MO (per IRB requirements)	No
Protocol departures/deviations/violations (per IRB 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	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 RSC or the MTN CORE. All distributions will include instructions related to IRB submission of the safety information.

Section 2. Protocol

This section contains a complete reference copy of the current version of the MTN-007 protocol and any protocol Clarification Memos (CM) and Letters of Amendment (LOA) for the current version of the protocol. To ensure that this manual continues to reflect current protocol specifications:

- Upon receipt of any protocol CM, place a copy of the memo in this section.
- Upon receipt of any protocol LOA, place a copy of the letter in this section.
- Upon receipt of any full protocol amendment, replace the protocol, CM, and LOA in this section with the amended protocol.

At the time of this printing, the following are the current protocol specifications:

- Protocol Version 2.0, dated 13 August 2010

Further information on the content and required handling of protocol Clarification Memos, Letters of Amendment, and Full Amendments is available in Section 9.2 of the MTN Manual of Operations.

MTN-007
A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

A Study of the Microbicide Trials Network

Funded by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
National Institute of Mental Health
US National Institutes of Health

Grant #:
5-U01-AI068633-05

DAIDS Protocol #: 10736

IND Holder:
CONRAD

This protocol will be performed under CONRAD IND#: 73,382

Protocol Chair:
Ian McGowan, MD, PhD, FRCP

Protocol Co-Chair:
Kenneth Mayer, MD

Version 2.0

August 13, 2010

MTN-007

A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

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LIST OF ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine transaminase
APV	amprenavir
ARV	antiretroviral
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
C_{max}	maximum plasma concentration
CAB	community advisory board
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	US Code of Federal Regulations
cGMP	current good manufacturing practices
CI	confidence interval
CRF	case report form
CRS	Clinical Research Site
CT	*Chlamydia trachomatis,* chlamydia
CTA	Clinical Trial Agreement
CVL	cervicovaginal lavage
DAIDS	Division of AIDS
ddC	zalcitabine
ddI	didanosine
DLV	delavirdine
DMPA	depot-medroxyprogesterone acetate
DNA PCR	deoxyribonucleic acid polymerase chain reaction
DSMB	Data and Safety Monitoring Board
EC_{50}	50% effective concentration
EAE	expedited adverse event
EIA	enzyme immunoassay
EFV	efavirenz
ET	Eastern Time
FDA	US Food and Drug Administration
FDR	false discovery rates
FTC	emtricitabine
g	gram
GC	*Neisseria gonorrhoeae,* gonorrhea

GCP	good clinical practice
GEE	generalized estimation equations
GLP	good laboratory practices
HBsAg	Hepatitis B surface antigen
HEC	hydroxyethyl cellulose
HIV	Human Immunodeficiency Virus
HPLC	high pressure liquid chromatography
HPTN	HIV Prevention Trials Network
hr	hour
HRA	high resolution anoscopy
HSV-2	Herpes simplex virus type 2
IATA	International Air Transport Association
IDV	indinavir
IFA	immunofluorescent antibody
IL	interleukin
IND	investigational new drug
IoR	Investigator of Record
IRB	Institutional Review Board
IV	intravenous
kg	kilogram
LDMS	Laboratory Data Management System
MDP	Microbicide Development Program
MIP	macrophage inflammatory protein
mL	milliliter
MMC	mucosal mononuclear cells
mRNA	messenger ribonucleic acid
MSM	men who have sex with men
MTN	Microbicide Trials Network
MTT	[1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan]
N-9	nonoxynol-9
NAAT	nucleic acid amplification testing
NE	neutrophil elastase
NFV	nelfinavir
ng	nanogram
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NL	Network Laboratory
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drugs
NVP	nevirapine
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PBS	phosphate buffered saline

PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PK	pharmacokinetics
PMPA	9-[(R)-2-(phosphonomethoxy) propyl] adenine monohydrate
PMPAp	PMPA monophosphate
PMPApp	PMPA diphosphate
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development
PrEP	pre-exposure prophylaxis
PRS	phone reporting system
PSRT	Protocol Safety Review Team
PSS	polystyrene sulfonate
PTID	Participant Identification Number
qc	quantitative competitive
qRT-PCR	quantitative real time reverse transcriptase polymerase chain reaction
RAI	receptive anal intercourse
RANTES	Regulated upon Activation-Normal T cell Expressed and Secreted
RMP	Rectal Microbicide Program
RNA	ribonucleic acid
RPR	rapid plasma reagin
RSC (DAIDS)	Regulatory Support Center
RT	reverse transcriptase
RT-PCR	reverse transcriptase polymerase chain reaction
RTV	ritonavir
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDF	stromal-derived factor
SDMC	Statistical and Data Management Center
SHIV	Simian/Human Immunodeficiency Virus
SIV	Simian Immunodeficiency Virus
SLPI	secretory leukocyte protease inhibitor
SMC	study monitoring committee
SOP	standard operating procedure
SQV	saquinavir
STI	sexually transmitted infection
T_{max}	time to peak concentration
$TCID_{50}$	50% Tissue Culture Infective Dose
TDF	tenofovir disoproxil fumarate (oral tenofovir)
TER	transepithelial resistance
TERIS	Teratogen Information System
TFV	tenofovir gel
Th	T helper
UCLA	University of California at Los Angeles
ULN	upper limit of normal

VI	virus isolation
VM	vaginal microbicide
vRNA	viral ribonucleic acid
WB	western blot
w/v	weight per volume
w/w	weight for weight
ZDV	zidovudine
µCi	microcurie
µg	microgram
µL	microliter
µM	micromole

MTN-007

A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

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A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

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MTN-007

A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

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MTN-007

A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

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MTN-007

A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

INVESTIGATOR SIGNATURE FORM

Version 2.0
August 13, 2010

A Study of the Microbicide Trials Network (MTN)

Funded by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
National Institute of Mental Health
US National Institutes of Health

IND Holder:
CONRAD

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 product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified. 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 CONRAD Inc. 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-007

A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

PROTOCOL SUMMARY

Short Title:	**Tenofovir Rectal Safety Study**
Clinical Phase:	1
IND Sponsor:	CONRAD
Protocol Chair:	Ian McGowan, MD, PhD, FRCP
Protocol Co-Chair:	Kenneth Mayer, MD
Sample Size:	Approximately 60
Study Population:	RAI (receptive anal intercourse)-abstinent, HIV-uninfected adults (male and female) from sites listed below

Participating Clinical Research Sites (CRS):

- Alabama Microbicides CRS, Birmingham, AL
- Fenway Clinic CRS, Boston, MA
- Pittsburgh CRS, Pittsburgh, PA

Study Design:	Phase 1 randomized, double-blinded, multi-site, placebo-controlled trial
Study Duration:	Participant accrual will take approximately 5 months and each participant will be on study for approximately 4 to 11 weeks. The total duration of the study will be approximately 8 months.

Study Products:

<u>Rectal</u>

- Tenofovir 1% gel
- 2% Nonoxynol-9 gel (Gynol-II®)
- Placebo gel (hydroxyethylcellulose-HEC)

Study Regimen:

After completing screening and baseline evaluation, eligible participants will be randomized to receive tenofovir 1% gel, 2% nonoxynol-9 gel (N-9) or placebo gel (15 per group). The study will also include a no treatment arm (15 participants). Participants will return to the clinic, where they will self-administer a single dose of the study gel under observation. Within approximately 30 minutes, lavage, stool, and rectal biopsy specimens will be obtained. After a one-week recovery period, participants will return to the clinic for assessment. If no significant adverse events (AEs) are reported they will begin to self-administer once-daily outpatient doses of the study gel for 7 days. Participants will return to clinic for evaluation and specimen collection after completion of 7 days of daily dosing.

Primary Objective:

- To evaluate the safety of tenofovir 1% gel when applied rectally

Primary Endpoint:

- Grade 2 or higher AEs as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and/or Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies) to this table

Secondary Objectives:

- To evaluate the acceptability of tenofovir 1% gel when applied rectally
- To evaluate the safety of the placebo gel when applied rectally
- To determine whether use of tenofovir 1% gel is associated with rectal mucosal damage
- To determine whether use of 2% nonoxynol-9 gel (Gynol-II®) is associated with rectal mucosal damage

Secondary Endpoints:

- The proportion of participants who at their Final Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during receptive anal intercourse
- Grade 2 or higher adverse events in the placebo gel arm, as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August

2009) and/or Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies)

- Changes in the following parameters:

    - Epithelial sloughing
    - Intestinal histopathology
    - Intestinal mucosal mononuclear cell phenotype
    - Intestinal mucosal cytokine messenger RNA (mRNA)
    - Intestinal mucosal gene expression arrays
    - Cytokine profile in rectal secretions
    - Fecal calprotectin
    - Microflora

Exploratory Objectives:

- To determine whether regional heterogeneity exists between mucosal endpoints in samples collected at 9 cm and 15 cm for all parameters examined

- To determine whether there is a correlation between histological abnormality and changes in mucosal biomarkers

Exploratory Endpoints:

- Changes in the following parameters:

    - Epithelial sloughing
    - Intestinal histopathology
    - Intestinal mucosal mononuclear cell phenotype
    - Intestinal mucosal cytokine messenger RNA (mRNA)
    - Intestinal mucosal gene expression arrays
    - Cytokine profile in rectal secretions
    - Fecal calprotectin
    - Microflora

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel
MTN Protocol Number:	MTN-007
Short Title:	Tenofovir Rectal Safety Study
Date:	August 13, 2010

1.2 Sponsor and Monitor Identification

Funding Agency:	Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID)/National Institute of Mental Health (NIMH)/National Institutes of Health (NIH) 6700 B Rockledge Drive Bethesda, MD 20892 USA
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2 INTRODUCTION

2.1 Background of Microbicide Research

To date, the majority of microbicide research has focused on the assessment of the safety and effectiveness of vaginal microbicides used for the prevention of HIV transmission via the vaginal compartment. Receptive anal intercourse (RAI) is common among men who have sex with men (MSM) and there is increasing evidence that heterosexual women in the developed and developing world also practice anal sex (Table 1). It can therefore be anticipated that once vaginal microbicides are licensed, they will be used in both the vaginal and rectal compartments. As a consequence, there is a need to evaluate both the rectal and vaginal safety profiles of candidate microbicides.

Table 1: Summary of RAI in Surveys of Sexual Behavior

Population	Men, Women, or Men and Women	N	Prevalence of RAI	Reference
MSM in EXPLORE study	Men	4,295	48-54%	Koblin et al. 2003[1]
High risk women	Women	1,268	32%	Gross M et al. 2000[2]
College students	Men and women	210	20%	Civic D 2000[3]
US Survey (15-44 year olds)	Men and women	12,571	35-40%	Mosher 2005[4]
Californian residents	Men and women	3,545	6-8%	Erickson PI et al. 1995[5]

The Rectal Microbicide Program (RMP-02)/MTN-006 and MTN-007 clinical protocols have therefore been developed to assess the safety and pharmacology of tenofovir gel when used rectally in men and women as well as address critical questions in rectal microbicides through explorative objectives. Although a single combined study was considered, the complexity of the study and the potential participant burden were considered to be substantial and as a result the protocol teams felt compartmentalization of key activities into two concurrent and mutually supportive clinical studies was a more efficient, less burdensome and safer approach. RMP-02/MTN-006 concentrated on systemic, mucosal and tissue pharmacology and pharmacodynamics of tenofovir 1% gel following administration, including *ex vivo* challenge of biopsies with HIV as a potential marker for retained tissue anti-HIV activity. MTN-007 will focus on accumulating Phase I safety and acceptability data, while providing in its secondary and exploratory objectives the data needed to determine maximum and minimum parameters for a suite of potential rectal safety assays using comparisons of the results from the Gynol II® (2% N-9), placebo, and no treatment arms. In order to assure comparability both protocols have been operationally (general schema, procedures, inclusion and exclusion criteria, etc.) harmonized. The trials also have in common the basic suite of rectal safety assays, which have been developed by

the University of California at Los Angeles (UCLA) Microbicide Development Program (MDP) team. Together these two trials should act synergistically to determine/establish: (1) initial safety of tenofovir 1% gel as a rectal microbicide; (2) acceptability of a vaginally formulated tenofovir gel when used rectally; (3) pharmacokinetics (PK)/ pharmacodynamic (PD) parameters for rectal tenofovir 1% gel use; and (4) further validate the proposed rectal safety suite by establishing maximum (Gynol II®), minimum (placebo gel), and baseline (no treatment arm) mucosal responses, while proactively managing participant and clinical site burden. Additionally, the co-sponsorship of the RMP-02/MTN-006 trial (UCLA and University of Pittsburgh sites) will support the transition of the UCLA site–developed safety suite to the MTN Network Laboratory (NL) (RMP-02/MTN-006), which will then disseminate the suite to the MTN-007 sites.

Vulnerability of the Rectal Compartment to HIV Infection

The rectal compartment is highly vulnerable to HIV transmission. A single layer of columnar epithelium separates the intestinal lumen from the lamina propria. The lamina propria is populated with a broad range of HIV target cells including macrophages, dendritic cells, and activated CD4+ T lymphocytes expressing the CCR5 and CXCR4 HIV-1 coreceptors.[6] It is likely that the immune composition of the rectal mucosa is at least partially responsible for the 10- to 20-fold increased risk of HIV transmission associated with anal[7, 8] compared to vaginal intercourse.[9, 10] Any product that induces local inflammation is likely to further increase this risk by recruiting and/or activating the immune target cells.

Developing Safety Standards for Rectally-Administered Microbicides

Methods to assess microbicide induced toxicity in the rectal compartment are in a state of evolution. Mucosal changes may be subtle and require new modes of detection (polymerase chain reaction (PCR), flow cytometry, immunohistochemistry, etc). For this reason, the HIV Prevention Trial Network (HPTN) sponsored the HPTN 056 study "Characterization of Baseline Mucosal Indices of Injury and Inflammation in Men For Use in Rectal Microbicide Trials" conducted at UCLA.[11] The lessons learned from the HPTN 056 trial have guided the selection of parameters to be included in this protocol. As these are assays in development and clinical relevance remains to be defined, these will not be safety indices but exploratory endpoints. The rationale for selecting each of these endpoints is further described below:

Epithelial sloughing

Rectal lavage and examination of effluent for shedding of epithelial cells has been used to characterize the rectal safety profile of microbicide candidates in murine, non-human primate, and human studies. This approach has demonstrated that N-9 is associated with transient epithelial disruption. Substantial reversal of these mucosal changes occurred by 2 hours and microscopically normal epithelium was noted after 24 hours.[12-14] In contrast, administration of VivaGel®, C31G, Carraguard, or UC781 to non-human primates did not result in epithelial desquamation.[15-18] Since the epithelial sloughing does not have an absolute, quantifiable threshold, the scoring system of 0-to-4 will be used.[16] Each of four petri-dish quadrants is scored as either 0 or 1, indicating either the

absence or presence of epithelial sheets. The total score for each preparation can therefore be from 0-4. Changes pre- and post-treatment will be analysed.

Intestinal histopathology

Histopathological assessment of intestinal tissue is a routine method of demonstrating mucosal abnormality associated with gastrointestinal diseases such as ulcerative colitis, Crohn's disease, and gluten enteropathy (celiac disease). In general, mucosal change in these diseases can be quite dramatic whereas microbicide-induced changes may be quite subtle. As a consequence we will use a qualitative scoring system (See Appendix V) developed by the inflammatory bowel disease community[19] and adapted for use in HPTN 056.[11] Prior to the HPTN 056 study, one rectal microbicide study using histological data,[14] employed a simple scoring system of normal, slightly abnormal, or abnormal. Using this histological system, 69% of the placebo recipients and 89% of the N-9 recipients had slightly abnormal or abnormal rectal biopsies. The scoring system developed for the HPTN 056 study might provide better discrimination between abnormal and normal histology.

Intestinal mucosal mononuclear cell phenotype

Enzymatic digestion of intestinal biopsies and flow cytometric analysis of T cell populations[20] will be used to determine if product administration is associated with changes in mucosal T cell populations, co-receptor expression, or T cell activation. Co-receptor expression (e.g., CCR5, CXCR4, etc.) on mucosal T cells is important for HIV-1 entry. In healthy HIV-1 seronegative individuals, the expression level of CCR5 is increased seven-fold in mucosal mononuclear cells (MMC) compared to peripheral blood mononuclear cells (PBMC).[6] CXCR4, however, is expressed in CD45RO+ T cells in similar levels as in MMC and PBMC. It was recently shown that MMC are more easily infected with HIV-1 than PBMC.[21, 22] Explanations for the high susceptibility of MMC to HIV-1 may include the increased expression of HIV-1 co-receptors, especially CCR5, as well as the heightened activation status of the MMC. The expression of CCR5 has been shown to be up-regulated by pro-inflammatory and T helper (Th)-1 cytokines, while Th-2 cytokines up-regulate CXCR4.[23, 24] This suggests that expression of CCR5 and CXCR4 is partly controlled by Th1/Th2 type of cytokines, which have been shown to be up-regulated in rectal mucosa from HIV-infected patients.[11] It will be important to ascertain whether microbicidal agents trigger similar responses and associated increased vulnerability to HIV infection.

All flow cytometry will be performed at the MTN Core Laboratories in Pittsburgh, PA. This approach has been used before by other investigators[25, 26] and it is anticipated that it will be possible to conduct adequate assessment of mucosal T cell populations on these samples.

Intestinal mucosal cytokine mRNA

Documentation of an increase in mucosal production of pro-inflammatory cytokines such as interleukin (IL)-6 or IL-8 following microbicide exposure may act as a surrogate marker of product induced toxicity.[27] Recent work has helped define the optimal methodology to measure cytokines in biological samples.[28] In MTN-007 we will

measure proinflammatory cytokines that have been associated with increased recruitment of potential HIV target cells and/or replication of HIV infection. Previous HIV mucosal pathogenesis studies have demonstrated significant increases in mucosal cytokine mRNA in individuals with untreated HIV infection compared to controls or patients with undetectable plasma HIV viremia.[29, 30]

CCL5, also known as Regulated upon Activation-Normal T Cell Expressed and Secreted (RANTES), macrophage inflammatory protein (MIP)-1α and MIP-1β13 are the natural ligands for CCR5 while stromal-derived factor (SDF) -1 is the ligand for CXCR4. The physiological function of β-chemokines and their receptors is to direct migration of recruited lymphocyte subsets to sites of inflammation and immune activation furthering the inflammatory cascade. Blocking chemokine activity has proved to be effective for inhibiting the migration of certain leukocytes while up-regulation of chemokine receptors and their ligands are characteristic correlates of mucosal inflammation.[31, 32] Immune activation of resting $CD4^+$ T cells has been shown to trigger viral replication and spread.[33, 34]

In MTN-007 we will use quantitative, real-time reverse transcriptase polymerase chain reaction (qRT-PCR) to quantify mucosal mRNA expression of the following proinflammatory cytokines, chemokines, and chemokine receptors: IL-1β, IFN-γ, TNF-α, IL-6, IL-8, IL-12, IL-17, IL-23, MIP-1α, MIP-1β, RANTES, and CCR5.

Cytokine profile in rectal secretions

As discussed above, measurement of cytokines or chemokines in mucosal tissue or local secretions may provide important information regarding the potential for a candidate microbicide to induce mucosal toxicity. In addition to the mRNA analysis of intestinal tissue biopsies, we will quantify cytokine levels in rectal secretions using the Luminex® technique, which can measure multiple cytokines or chemokines in small volumes (< 100 μL) of rectal secretions. We will use Luminex® to measure the following cytokines, chemokines, and chemokine receptors: IL-1β, IFN-γ, TNF-α, IL-6, IL-8, IL-12, IL-17, IL-23, MIP-1α, MIP-1β, RANTES, and CCR5.

Intestinal mucosal gene expression arrays

Currently, no validated biomarkers that reliably measure the genital toxicity of microbicides are available. Certain cytokines and chemokines may in principle be suitable as mucosal biomarkers for microbicide-induced toxicity or inflammation. The concentration of inflammatory cytokines in mucosal secretions has therefore been evaluated in prior microbicide studies. However, these studies have their limitations. First, only a few genes/proteins can be studied from one sample. Second, it is unclear what constitutes a meaningful change in cytokine concentration.

Because of the described limitations when measuring individual biomarkers, it would be useful to develop assays that evaluate the cumulative impact of candidate microbicides on mucosal immune function as a whole. To evaluate the global impact of microbicides on the mucosa, we will perform gene expression microarrays on mRNA isolated from mucosal biopsies taken before and after application of tenofovir, N-9 or placebo gel.

HumanWG-6 Expression BeadChips (Illumina Inc., San Diego, CA) permit the measurement of 48,000 mRNAs simultaneously on a single high-density oligonucleotide microarray. This offers the opportunity to: (1) identify signature expression patterns of dozens or even hundreds of genes that correlate with microbicide side effects on the mucosa; (2) interpret expression changes of a particular gene group, such as inflammatory cytokines, in relationship to other genes; and (3) cross-validate the array results with measurements of mucosal cytokine mRNAs by RT-PCR and of cytokine proteins in mucosal secretions by the Luminex® technique (both performed in other participating laboratories).

An expected outcome of the array studies is the identification of groups of genes, in particular apoptotic, pro-inflammatory and/or innate immunity-related genes, which are modulated significantly from baseline in response to topical N-9 application. In comparison, these changes are expected not to occur after tenofovir or placebo gel application. Another expected outcome of the array studies is the validation of any significant cytokine/chemokine/chemokine receptor changes found by qRT-PCR and Luminex® measurements. Similar results in all three assays (expression array, qRT-PCR and Luminex®) will underscore the potential usefulness of a biomarker to predict toxicity of a candidate microbicide. Moreover, interpreting such a promising marker in the light of other gene expression changes in the microarray will provide an opportunity to better understand its biological significance.

Fecal calprotectin

Stool samples will be collected at the time of rectal lavage for the measurement of fecal calprotectin. Calprotectin accounts for 60% of the cytoplasmic protein fraction of polymorphonuclear granulocytes and is also found in monocytes, macrophages, and eosinophils.[35, 36] Calprotectin plays an important role in innate immunity and has antibacterial, antifungal, and immunomodulatory effects *in vivo*. Because intestinal granulocytes end their lifespan by migrating through the intestinal wall and since granulocyte-derived calprotectin can be found in feces, calprotectin is felt to be a useful indirect index of mucosal inflammation.[37, 38] In fact, fecal calprotectin levels are elevated in inflammatory bowel disease[39, 40] and correlate well with disease activity in Crohn's disease and ulcerative colitis. In addition, fecal calprotectin levels have been found to be significantly elevated in first-degree relatives of patients with Crohn's disease even though all the relatives were clinically asymptomatic.[41] These data suggest that the fecal calprotectin assay may be sufficiently sensitive to respond to subtle increases in mucosal inflammation. Fecal calprotectin has a sensitivity of 96% in discriminating between healthy controls (2mg/L; 95% CI 2-3 mg/L) and subjects with active inflammatory bowel disease (91 mg/L; 95% CI 59-105 mg/L).[40]

Microflora

Assessment of pre- and post-exposure changes in rectal microflora will be conducted. It is currently unknown whether rectal administration of tenofovir 1% gel will prompt a change in the rectal microflora. Transient reductions in vaginal lactobacilli have been noted with the administration of candidate microbicides.[16] There are no rectal microflora data from human microbicides although non-human primate studies have not

demonstrated significant changes in rectal microflora following rectal administration of vaginal microbicides.

Assessing Acceptability of Rectally-Administered Microbicides

Prevention tools are effective only if used. The limited use of condoms by many at-risk individuals illustrates the importance of a product's acceptability and perceived need, i.e., the willingness of the users of the product to use it correctly and consistently. This study will explore the acceptability of tenofovir 1% gel for rectal use by means of a behavioral assessment that includes both structured and semi-structured methods. This assessment will evaluate not only product acceptability, but also the acceptability of a vaginal applicator for rectal product application. The behavioral assessment consists of two elements: 1) a Baseline Behavioral Questionnaire and 2) a Product Acceptability Questionnaire. The questionnaires were originally developed based on in-depth qualitative interviews of 20 participants in the first phase of R01 HD046060 "Topical Microbicide Acceptability," (Carballo-Diéguez, PI), a study that focused on acceptability of rectal microbicides among men and women.[42, 43]

The questionnaires were subsequently administered to more than 100 MSM in Boston and New York, and to 36 men and women participating in a rectal microbicide study in Los Angeles (Peter Anton, PI). This study showed that there were no comprehension problems or other difficulties. There are additional advantages to using the same product-acceptability instrument across studies, since this allows more valid post-hoc comparisons across studies.

2.2 Description of Study Products

2.3 Tenofovir 1% Vaginal Gel (Tenofovir Gel)

Tenofovir (sometimes referred to as PMPA,9-[(R)-2-(phosphonomethoxy)propyl] adenine monohydrate) is a novel nucleotide analogue belonging to the class of acyclic phosphonomethylether nucleotides with potent activity against retroviruses.[44] Further information is available in the current version of the tenofovir gel investigator's brochure.[44]

2.3.1 Mechanism of Action

Tenofovir is an acyclic nucleotide analogue of adenosine monophosphate. Once inside the cell tenofovir is phosphorylated by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate is a competitive inhibitor of HIV-1 RT that terminates the growing DNA chain. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

2.3.2 Strength of Study Product

The strength of the tenofovir gel will be the concentration (1%) previously tested in HPTN 050 (investigational new drug (IND 55,690)), CAPRISA-004, CONRAD A04-095

(IND 73,382) and A04-099 (IND 73,382), HPTN 059 (IND 55,690), MTN-001 (IND 55,690), MTN-002 (IND 55,690), and RMP-02/MTN-006 (CONRAD IND 73,382). From the current good manufacturing practice (cGMP) formulators (DPT Pharmaceuticals), the density of the gel is 1.06 g/mL which has been rounded up to 1.1 g/mL of gel. Each gram of gel contains 10 mg of tenofovir, resulting in a total of 44 mg of tenofovir delivered in each application (or 0.044 grams of tenofovir).

2.4 2% Nonoxynol-9 Gel

N-9 is a non-ionic surfactant that has been most commonly used as a spermicidal agent in several over-the-counter products including condoms, gels, and films.

2.4.1 Mechanism of Action

N-9 is a non-ionic surfactant that destroys the integrity of the lipid bilayer membrane with a virucidal action that disrupts the viral envelope. It is by this mechanism that N-9 has its effect on HIV-1.[45, 46]

2.4.2 Strength of Study Product

The strength of the study product will be 2%. This strength has been used in previous human studies of this compound and is one of the strengths currently marketed as a spermicidal gel in North America. Murine (2% to 3.5% N-9)[13], nonhuman primate (4% N-9)[47] and human (2% N-9)[12] rectal studies demonstrated acute transient epithelial disruption and sloughing at these doses. In a study by Tabet et al.[14], in which participants received a 3.5% formulation of N-9 in escalating doses over a 6-week period, minor histological abnormalities were commonly observed.

2.5 Placebo Gel

The placebo gel is the hydroxyethylcellulose (HEC)-based or "Universal" placebo gel,[48] a vaginal product that contains HEC as the thickener, purified water, sodium chloride, sorbic acid and sodium hydroxide. The placebo gel is used to approximate the viscosity of other microbicide gel candidates.

2.5.1 Mechanism of Action

The placebo gel is designed to be inactive in the vagina. The gel is isotonic and formulated at a pH of 4.4 to avoid disrupting the normal vaginal pH. It is formulated with minimal buffering capacity to avoid the inactivation of sexually transmitted pathogens.

2.5.2 Strength of Study Product

Placebo gel at a concentration of 2.7% w/w HEC will be used in this study.

2.6 *In Vitro* Studies

2.6.1 Reformulated Tenofovir Gel

The reformulated tenofovir 1% gel being used in MTN-007 has a lower osmolality than the original formulation that was used in prior studies.[49] Additionally, the density of the reformulated tenofovir 1% gel is 1.02 g/mL. This will be the first clinical trial using this formulation of tenofovir 1% gel. Safety testing in epithelial cell lines has demonstrated retention of transepithelial resistance (TER) by Caco-2 and HEC-1-A cell lines. Previous results showed the original formulation to induce a transient drop in the epithelial resistance. This was not observed with the reformulated tenofovir gel. Safety testing of colorectal explants shows similar MTT (Formazan [1-(4, 5-dimethylthiazol-2-yl)-3, 5-diphenylformazan]) results with both formulations. However, histological testing showed retention of the epithelium after application of the reformulated tenofovir gel as compared to epithelial stripping with the original formulation. Additional testing in colorectal explant cultures also showed that the new formulation did not compromise product efficacy. Collectively, these data suggest that the reformulated tenofovir gel is just as effective as the original formulation but is less toxic to the epithelium.

2.6.2 Tenofovir

Formulation Testing

The physiological properties evaluated included osmolarity, viscosity, pH, and *in vitro* release.[50] In comparison to isosmolar standards, tenofovir 1% gel and its matched placebo exhibited 11.5-fold and 11-fold, greater osmolarity, respectively than isosmolar conditions implying that this formulation is hyperosmolar. Both gels had a pH of ~4.4, which is similar to the vaginal environment. Viscosity evaluations were conducted for both tenofovir 1% gel and its matched placebo gel. The viscosity of the tenofovir 1% gel and its placebo at 30 rpm showed reproducible results in 3 trials. Both gels were found to be shear thinning in nature. Thinning viscosity indicates that it is "flowable" which allows for even spread across mucosal surfaces.

Safety Testing in Cell Lines

Tenofovir 1% gel and its placebo gel were evaluated for its effect on the viability of colorectal Caco-2 epithelial cell line.[50] Viability of the Caco-2 epithelial cell line after a 24-hour exposure to tenofovir 1% gel or placebo gel showed minimal reduction; a 1:10 dilution of both gels yielded ≥ 60% viability. To put this into perspective, the over-the-counter preparations of N-9 (3%) and KY® jelly (Johnson & Johnson, New Brunswick, NJ) need to be diluted a minimum of 1:1000 and 1:100, respectively, of their original formulation to yield ≥ 60% viable epithelial cultures.[47] Using the 1:10 dilution, a "2 hours per day for 5 days" exposure experiment was performed to evaluate the impact of extended use on Caco-2 cell viability. No reduction in Caco-2 viability was noted after the 5-day exposure, indicating that the 1:10 dilutions of both gels were stable concentrations for use in further analysis.

The ability of mucosal epithelial cells to maintain an intact, polarized monolayer in the presence of a microbicide is a possible predictor of that product's safety on colorectal tissues because the epithelial layer is integral in the protection against sexually transmitted infections including HIV. Therefore, Caco-2 cells were plated in duplicate in transwell plates, and their TER was measured using the Millicell® ERS meter (Millipore, Billerica, MA) to form a polarized monolayer. When the cells reached plateau TER, a 1:10 dilution of tenofovir 1% gel or placebo gel and a 1:50 dilution of N-9 were added to the apical side of the transwells. The TER was measured over a 24-hour period. Tenofovir 1% gel and placebo gel maximally reduced the TER as compared to the control (68% and 59% respectively) after 4 hours. Over the next 20 hours, the TER returned to control TER levels. N-9-treated wells, however, continually declined and reached background levels after 4 hours. These data suggest that hyperosmolar nature of the tenofovir 1% gel formulation resulted in the transient loss of the epithelial monolayer resistance.

Safety Testing in Colorectal Explant Cultures

Tenofovir 1% gel and its matched placebo were tested for toxicity to colorectal explant cultures.[50] Briefly, duplicate polarized tissues were exposed to product for 18 hours and then washed to remove excess product. One of the duplicate tissues was incubated with MTT to measure the reduction to formazan and the other was placed in 10% buffered formalin for histology. Up to 5 different tissue donors were used. Tenofovir 1% gel and the placebo did not reduce the viability of the colorectal explants as based on the MTT assay. When assessed for histologic changes, the tenofovir 1% gel and to a lesser extent the placebo treated tissues showed fractured epithelium with an intact lamina propria. This result may be due to the hyperosmolar formulation of the tenofovir 1% gel and this data would correspond to the changes noted for the epithelial cell line TER.

Efficacy Testing in Colorectal Explant Cultures

The efficacy of the tenofovir 1% gel and placebo gels were assessed using the polarized colorectal explant culture system.[50, 51] The explants were set-up in duplicate and exposed to HIV-1 without or with 1:5 dilutions of tenofovir 1% or placebo gels on the apical side. The explants were allowed to culture overnight and then washed. The explants were followed for 21 days and HIV-1 replication was assessed by the production of p24 in the basolateral supernatant. The tenofovir 1% gel was effective at preventing HIV-1 infection of the tissue. The placebo was also partially effective at reducing the HIV-1 infection. This has been noted previously for other products that were evaluated.[51]

Anti-HIV-1 Activity

The *in vitro* antiviral activity of unformulated tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes.[52, 53] The 50% effective concentration (EC_{50}) values for tenofovir were in the range of 0.04 µM - 8.5 µM. In drug combination studies of tenofovir with NRTIs (abacavir [ABC], didanosine [ddI], lamivudine [3TC], stavudine [d4T], zalcitabine [ddC], zidovudine [ZDV]); non-nucleoside

reverse transcriptase inhibitors (NNRTI) (delavirdine [DLV], efavirenz [EFV], nevirapine [NVP]); and protease inhibitors (amprenavir [APV], indinavir [IDV], nelfinavir [NFV], ritonavir [RTV], saquinavir [SQV]), additive/synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values 0.5 µM - 2.2 µM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 µM to 5.5 µM).

Resistance

HIV-1 isolates with reduced susceptibility to unformulated tenofovir have been selected *in vitro.*[53, 54] These viruses expressed a K65R mutation in RT and showed a 2-4 fold reduction in susceptibility to tenofovir. Of note, this mutation also confers increased susceptibility to some other nucleoside reverse transcriptase inhibitors (NRTI), and is associated with approximately 50% reduction in the replicative capacity of HIV-1 (potentially resulting in a "less fit" virus).[55] Tenofovir-resistant isolates of HIV-1 have been recovered from some patients treated with Viread® in combination with certain antiretroviral (ARV) agents.[53] In treatment-naïve patients, 8/47 (17%) isolates from patients failing Viread® + 3TC + EFV through week 144 showed >1.4 fold (median 3.7) reduced susceptibility *in vitro* to tenofovir.

Cross-resistance

Cross-resistance among certain NRTIs has been recognized.[52, 53] The M184V/I and/or K65R substitutions selected *in vitro* by the combination of emtricitabine (FTC) and unformulated tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either 3TC or FTC, and either abacavir, didanosine, or zalcitabine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions. In treatment-experienced patients, 14/304 (5%) isolates from patients failing Viread® through week 96 showed >1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution. HIV-1 isolates from patients (n = 20) whose HIV-1 expressed a mean of 3 ZDV-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.[54]

2.6.3 2% Nonoxynol-9 Gel

Formulation Testing

None has been done. The 2% N-9 gel was purchased in a local pharmacy.

Safety Testing in Cell Lines

Colorectal epithelial cell lines, Caco-2 and SW837, were exposed to 10-fold dilutions of the gel for 24 hours.[56] The dilution that resulted in greater than 60% viability was 1:1000 which equates to 20 µg/mL of N-9 (20 mg/mL in original gel). Using this dilution of 2% N-9 gel, no significant impact in the Caco-2 transepithelial resistance was noted. However, if the dose was 2 mg/mL (1:10 dilution of the original gel), the monolayer

resistance was completely destroyed by 2 hours after application. These data suggest that significant dilution of the N-9 gel is required to not be toxic to the colorectal epithelial cell lines.

Safety Testing in Colorectal Explant Cultures

Colorectal explant tissue was set-up in duplicate in a polarized transwell system. Two percent N-9 gel diluted to 2 mg/mL or placebo gel was applied to the apical side of the tissue and allowed to culture overnight.[51] After culture, the tissues were washed and one of the duplicates was placed in formalin for histological analysis and the other was placed in 1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan (MTT) to determine viability (adenosine triphosphate (ATP) activity). Complete necrosis of the epithelium and lamina propria was observed in N-9-treated explants. Explants treated with each placebo were histologically normal. Exposure to N-9 produced the greatest reduction in viability, to 47% of that of the control (P<.052). Explants treated with the placebo gel were not significantly different from the control. Collectively, these data show that 2% N-9 gel was very toxic to the colorectal explant tissues.

Anti-HIV-1 Activity

To assess the anti-HIV-1 activity, 2% N-9 gel was diluted 1:1000 to 20 µg/mL and applied to peripheral blood mononuclear cells (PBMCs) with HIV-1 isolates that included laboratory isolates (HIV-1_{BaL} and HIV-1_{LAI}) and 3 primary isolates (one each of subtype A, C, and CRF01-AE).[56] HIV-1 replication was detected using an HIV-1 p24gag ELISA from collected culture supernatants. The diluted N-9 completely inhibited HIV-1_{BaL}, subtype A, and subtype CRF01-AE infection but had 1 $\log_{10}$ reduction against HIV-1_{LAI} or subtype C (58% and 88% inhibition, respectively). Moreover, the placebo gel was equally as effective against HIV-1_{BaL} as the diluted 2% N-9 gel but was not effective against the other subtypes.

Colorectal explant tissue was set-up in a polarized transwell system and 2% N-9 gel diluted to 2 mg/mL or placebo gel were mixed with HIV-1_{BaL} and applied to the apical side of the tissue and allowed to culture overnight.[51] After culture, the tissues were washed and HIV-1 replication was monitored by the HIV-1 p24gag ELISA in the basolateral supernatant of the explant cultures. No HIV-1_{BaL} was recovered from the N-9-treated tissue due to the lack of viable immune cells to support viral replication. The placebo gel had minimal impact on HIV-1 infection of the tissue.

2.6.4 Placebo Gel

Formulation Testing

Analyses of pH (placebo gel mixed with human seminal plasma, 8.03 ± 0.26) found that the gel formulation did not show significant buffering capacity and could not acidify the alkaline pH of seminal plasma, a favorable property for a placebo formulation.[57] *In vitro* assessments of spermicidal activity utilizing human semen from healthy donors showed that the placebo gel had no significant deleterious effects on sperm motility, even after 60-minute incubation.

Safety Testing in Cell Lines

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).[48] Exposure of human vaginal epithelial cells to the HEC gel resulted in minimal IL-1α induction, even at the lowest dilutions tested (lowest dilution, 1:2). Additional studies have shown that HEC gel is safe to peripheral blood mononuclear cells, and colorectal epithelial cell lines.[51, 56] Indeed, no changes in the transepithelial resistance was noted after HEC gel was applied.[56]

Safety Testing in Colorectal Explant Cultures

The HEC gel was applied to colorectal explant tissues using a polarized system.[51] For safety analysis the MTT assay and histology were performed. No observed reduction in the MTT levels or changes in the tissue architecture were noted.

Efficacy Testing

Analysis of HEC gel activity against HIV showed that it had no protective effect when tested on PBMCs, macrophages, or colorectal explant cultures.[51, 56]

2.7 Condom Compatibility Studies

2.7.1 Tenofovir 1% Gel

The compatibility of tenofovir 1% gel was also tested with three types of lubricated male latex condoms.[44] A matched placebo gel and placebo gel (HEC gel as planned for this trial) were used as comparator gels. The condoms tested were representatives of leading brands on the US market (Trojan® and Durex®) with either silicone or aqueous lubricant. The airburst test was used to evaluate changes in film integrity (strength) and test specimens were measured before and after treatment with the gels to assess changes in strength properties following the application of the three gel preparations. All three gels were shown to be compatible with the above condoms. The compatibility of tenofovir 1% gel with Alatech™ Healthcare (Eufala, AL) male latex silicone lubricated condoms was also evaluated. Tenofovir placebo gel was used as a comparator. The two application treatments of tenofovir 1% gel and matched placebo gel increased airburst volumes by 5 to 6 L compared with the baseline. With an increase in volumes there was a decrease in airburst pressures by 0.2 kPa. This implies a physical change to a more elastic condom. This slight change in physical properties suggests an interaction of the tenofovir 1% gel with the silicone lubricant, but does not indicate that the condoms are unsuitable for use in clinical studies.

2.7.2 2% Nonoxynol-9 Gel

Nonoxynol-9 has been used as a condom coating for many years without any appreciable impact on condom function.

2.7.3 Placebo Gel

The effects of the placebo gel on three brands of condoms including Trojan Enz®, Durex® and Trojan Supra® have been evaluated.[44] The physical properties of each were not significantly affected. Although there were slight increases in airburst volume for all types, and an increase in pressure for synthetic condoms following gel exposure, this was considered normal and not statistically significant.

2.8 Animal Studies

2.8.1 Tenofovir 1% Gel

Pharmacokinetics-Vaginal Administration

Single-dose pharmacokinetics of radio-labeled tenofovir gel in female rabbits has been previously examined (0.5 mL, 1% w/v tenofovir, 5 mg per animal, 50 µCi/kg).[58] Plasma concentrations of radioactivity were highest at the first sample time point (0.5 hour (hr)) and below the level of quantification at 24 hours. Pharmacokinetic parameters including the proportion of dose absorbed systemically could not be estimated, due to the very low plasma concentrations.

In a tissue distribution study using the same radio-labeled tenofovir 1% vaginal gel formulation, dose and strength as the above study, eighteen female rabbits were administered an intravaginal dose using a gavage needle.[44] An additional eighteen rabbits received an intravaginal dose of 3% w/v radio-labeled tenofovir (15 mg per animal). Analysis of vaginal tissue sections found no clear relationship between tissue concentration and dose, with no consistent pattern of distribution. Very little radioactivity was recovered in non-vaginal tissues. Concentrations in blood (0.002 to 0.047 µg-eq/g of tissue) exemplified the variability of distribution of the product although the effect of oral absorption due to grooming behaviors of the animals may have impacted these results.

The pharmacokinetics, excretion and tissue distribution of ^{14}C-PMPA were evaluated in rats following intravaginal administration of an earlier formulation of tenofovir gel containing propylene glycol.[59] Four female rats received a single intravaginal dose administered as an aqueous gel containing 20 mg tenofovir/g. Plasma concentrations of total radioactivity were highly variable; this was attributed to inconsistent retention of the formulation within the vagina, or possibly oral absorption related to grooming. The apparent maximum plasma concentration (C_{max}) for tenofovir occurred at the earliest time point (15 minute), suggesting that absorption from the vagina was relatively rapid. Thereafter plasma concentrations declined with an approximate half-life of 1.6 hrs. The bioavailability of intravaginal tenofovir was estimated by comparison of the observed area under the curve $_{(0\text{-}24)}$ (AUC) with historical AUC data for an intravenous (IV) dose of 10 mg/kg tenofovir in rats (9.71 µg hr/mL). The observed systemic bioavailability of intravaginal tenofovir was 7.9%.

In the excretion and distribution study, two groups of four additional rats received a single intravaginal dose of ^{14}C-PMPA (10 mg/kg, 100 µCi/kg) administered as an aqueous gel containing 20 mg tenofovir/g. This study found that much of the dose was lost from the vaginal orifice by leakage. Vaginal tissue contained 0.1% of the dose and less than 0.01% of the dose was recovered in the ovaries and uterus.

The pharmacokinetics (PK) of radio-labeled tenofovir gel was evaluated via plasma and vaginal biopsies collected from four rhesus macaques following single-dose intravaginal administration of tenofovir 1% vaginal gel.[44] Radioactivity was detected starting at 15 minutes post application, with peak concentration of tenofovir in vaginal tissue at 8 hrs and remaining high at 12 hours. No significant radioactivity was detected in whole blood or plasma.

Systemic and vaginal tissue bioavailability was assessed in female white New Zealand rabbits following single and multiple intravaginal doses (twice a day for 7 or 14 days) of 1 mL of tenofovir 1% gel or a single IV solution of 10 mg tenofovir.[44] Animals that were vaginally and intravenously dosed were sacrificed at the following timepoints: 1) 8 hours after single IV dose; 2) 4 hours after single vaginal dose; 3) 8 hours after single vaginal dose; 4) 4 hours after the thirteenth twice-daily vaginal dose; and, 5) 4 hours after the twenty-seventh twice-daily vaginal dose (see table below). After sacrifice, vaginal tissue was rinsed to remove topical tenofovir, and biopsy samples were taken. Both vaginal rinse and vaginal tissue were analyzed for tenofovir content. Systemic absorption following a single intravaginal dose was barely detectable, and only within the first 30 minutes. Multiple intravaginal administrations of tenofovir 1% gel and the single IV administration of 10 mg tenofovir resulted in systemic levels of tenofovir (see Table 2).

Table 2: Tenofovir Bioassay Data

	Mean 1st Rinse Vaginal Surface (nanogram(ng)/mL)	**Mean Vaginal Tissue Concentration (ng/g)**	**C_{max} (ng/mL)**	**AUC (0-4 hr) (ng*hr/mL)**
Single IV, 8 hr	**362** (19-990)	**950** (120-5,019)	**10,221**	**4,013** (3,192-4,503)
Single vaginal, 8 hr	**97** (7-415)	**940** (10-7,277)	**3**	--
Single vaginal, 4 hr	**1,441** (2-5,100)	**2,817** (35-11,780)	**5**	--
Twice daily x 7d vaginal, 4 hr	**1,086** (145-4,369)	**3,146** (448-14,429)	**239** (29-808)	**342** (54-1,037)
Twice daily x 14d vaginal, 4 hr	**3,361** (33-8,000)	**11,409** (245-50,102)	**71** (24-197)	**94** (12-229)

Pharmacokinetics-Rectal Administration

Only preliminary assessments of single dose rectal administration of tenofovir 1% gel (PMPA) have been conducted in the setting of a pilot macaque efficacy trial.[60] Plasma samples were assayed for tenofovir concentration by the Clinical Pharmacology and Analytical Chemistry Core of the University of North Carolina Center for Acquired

Immunodeficiency Syndrome (AIDS) Research. Drug concentrations in plasma were determined by a validated high pressure liquid chromatography (HPLC) method with ultraviolet detection.[61] This method utilized a dynamic range of 10 to 10,000 ng/mL, with intra- and inter-day variability of <10% across this range. Total tenofovir concentrations were assayed in tissues using a fully validated HPLC method with mass spectrometry detection.

Analysis of intestinal tissue samples collected at necropsy showed that all tenofovir-dosed animals had measurable concentrations of drug in lysates of colorectal tissue at concentrations between 20.8 and 54.2 µg/g protein but no drug was detected in lysates of homogenates from the small intestine. Tissues from untreated animals acted as negative controls. To indirectly estimate the amount of intracellular phosphorylated tenofovir in tissues, samples were analyzed with (to measure the combination of tenofovir + tenofovir monophosphate + tenofovir diphosphate) and without (to measure tenofovir only) phosphatase hydrolysis. Subtracting the concentration of tenofovir obtained from tissue samples without phosphatase, from the concentration of tenofovir obtained from tissue samples with phosphatase, demonstrated that between 46-75% of total tenofovir in tissues was present as the intracellular monophosphate and diphosphate forms. Based on intracellular data describing tenofovir monophosphate: diphosphate ratios,[62-64] it was estimated that approximately 30-60% of total tenofovir in tissues was present as the intracellular diphosphate form. The relatively low rectal dose of tenofovir gel applied, an average of 10 µg/kg, resulted in a maximum plasma detection level of 0.19%, which was detected 15-minutes after rectal dosing.

Toxicology-Vaginal Administration

The preclinical toxicity of tenofovir gel has been evaluated in 14-day rat and 10-day rabbit vaginal irritation and toxicity studies.[58, 65] Daily intravaginal administration of tenofovir gel produced no vaginal irritation in rats (≤10% tenofovir) and minimal to mild vaginal irritation in rabbits (3% or 10% tenofovir).

14-Day Vaginal Irritation and Toxicity Study of Tenofovir Gel in Rats

Ten female Sprague Dawley rats/group received either 0% (vehicle control), 1%, 3%, or 10% tenofovir gel (2.5% HEC formulation) by intravaginal administration (0.5 mL/dose) once daily for 14 days.[44] There were no mortalities, and no tenofovir-related clinical signs of toxicity or changes in body weight, food consumption, or absolute/relative kidney weights. Individual and mean vaginal (gross) irritation scores for all tenofovir-dosed animals sacrificed at Day 15 were graded as 0 (no erythema or edema); microscopic irritation scores for the vagina, cervix, ovaries, uterine horns, and vulva were graded as 0 (normal histology). No tenofovir-related histopathological effects on the vagina, cervix, ovaries, uterine horns, vulva, or kidneys were observed.

10-Day Vaginal Irritation Study of Tenofovir Gel in Rabbits

The potential irritant effects of tenofovir were evaluated in vaginal tissues of female New Zealand White rabbits using three different gel formulations (2.5% HEC or 1.0 to 2.0% Carbopol® 1342).[44] This study consisted of eleven treatment groups (five rabbits/group) that received one of the following: a sham treatment or Conceptrol® (positive control);

0%, 0.3%, 1.0%, 3.0%, or 10.0% tenofovir formulated in the HEC gel preparation; or 0% or 3.0% tenofovir formulated in a 1.0% or 2.0% Carbopol® 1342 gel preparation. With the exception of the sham dose group, all rabbits received dose formulation (1.0 mL/dose) daily applied topically to the mucosal surface of the vaginal vault for 10 consecutive days. No mortalities and no tenofovir-related clinical signs of toxicity or body weight changes were observed in this study. Group composite vaginal irritation scores for the 10% tenofovir topical gel (HEC formulation), 0% tenofovir (1.0% Carbopol® 1342 formulation), and Conceptrol® (positive control) dose groups were each rated as "mild." Composite vaginal irritation scores rated "minimal" were observed for all other tenofovir, vehicle or sham treatment groups, regardless of the formulation. No unacceptable level of mucosal irritation was observed in any treatment group based on the protocol-derived criteria for this animal model. Generalized erosion and/or ulceration were observed only in animals receiving Conceptrol® positive control (two of five) or the 10% tenofovir topical gel (two of five).

Toxicology-Rectal Administration

14-Day Rectal Irritation Study of Tenofovir Vaginal Gel in Rabbits

Forty New Zealand White rabbits (approximately 10-12 weeks of age and weighing in the range of 2.0 to 2.5 kg at initiation of treatment) were assigned to five dose groups (one sham control, one placebo control and three active test article) consisting of four animals per sex per group under Good Laboratory Practices [(GLP) Pacific BioLabs, Hercules, CA]. The placebo control and active test articles consisted of tenofovir matched placebo gel and three different concentrations (1%, 3%, and 10%) of tenofovir gel respectively. The lubricant for the sham control group was K-Y Jelly from a commercial source.

All female animals were dosed for 14 days and all male animals were dosed for 15 days. Animals in Groups 2 to 5 received 1 mL doses of the respective placebo or test articles via rectal administration for 14/15 consecutive days. A short, soft catheter was attached to a syringe and filled with 1 mL of the appropriate test article. Animals in Group 1, (sham control) underwent the same treatment procedure for 14/15 days with the exception that no dose was administered and the catheter was lubricated with a non-irritating lubricant (K-Y Jelly) prior to insertion. The rectal route of administration was selected as it is the intended clinical route of administration.

Table 3: Rectal Irritation Study in New Zealand White Rabbits

Group	Intervention
1	sham
2	tenofovir placebo gel
3	tenofovir 1% gel
4	tenofovir 3% gel
5	tenofovir 10% gel

The test article, vaginally formulated tenofovir 1% gel, was well tolerated at dose concentrations (1 mL dose volume) of 1% (10 mg/dose), 3% (30 mg per dose) and 10% (100 mg per dose) when administered as a daily rectal dose for 14 days to female

rabbits or 15 days to male rabbits. There was no mortality in this study, and there was only one clinical finding that was potentially study-related: redness at the site of administration in one animal on one day of dosing. There was no evidence of a test article effect on body weight, body weight gain or food consumption over the dose period.

The test article, at the concentrations tested, was without significant effect at the rectal site of administration. Gross pathology at necropsy provided no evidence for tissue damage or inflammation of the rectum or surrounding tissues at the concentrations tested; histolopathological evaluation of the rectum and parts of the colon immediately adjacent to the rectum also showed no effect at the concentrations tested. Each rectum sample was subsectioned into proximal, mid and distal sections (in relation to the site of test article application) for histopathological analysis. Within each section, at least 5 subsections were evaluated for inflammation and other types of lesions. As mentioned, no differences were seen.

Rectal administration of the test articles produced little evidence of test article related systemic effects, despite measurable systemic exposures to tenofovir. At necropsy, gross pathology provided no *in situ* evidence for tissue damage or target organ effects. Changes in several hematology, coagulation and clinical chemistry parameters that reached statistical significance were not considered test article related because they were typically sporadic, not dose-related, and were present in only one gender of rabbit on each occasion. Organ weight changes also reached statistical significance on occasion, but these were also considered not to be test article related for the same reasons cited above, i.e., sporadic and not dose-related. No tissues or organs other than the rectum and colon were examined for histopathological changes.

Rectal application of test articles resulted in measurable systemic concentrations of tenofovir at all dose levels, and after the first dose on Day 1 and the Day 14 dose. Tenofovir exposures were variable on Day 1; however, by Day 14 plasma concentrations were more consistent amongst individual animals and there was a clear dose-related increase in tenofovir exposures in both male and female rabbits. Systemic exposures to tenofovir were comparable in female and male rabbits. Absorption of tenofovir was relatively rapid, with the plasma T_{max} occurring at 1 hr on Day 1 (for most dose groups) and at 2 hr (female rabbits) and 4 hr (male rabbits) on Day 14. Mean C_{max} values on Day 1 ranged from 11.7 ng/mL (Group 4 females) to 59.0 ng/mL (Group 3 females), except Group 3 males where the C_{max} was 1182 ng/mL. Mean C_{max} values on Day 14 ranged from a low of 32.3 ng/mL (Group 3 males) to 265 ng/mL (Group 5 males). The mean T_{max} and C_{max} values for Group 3 males on Day 1 were skewed by one male rabbit with a very high tenofovir plasma concentration at 24 hr post dose of 4210 ng/mL. The elimination half-life for tenofovir could not be determined with accuracy due to the variable exposures on Day 1, and a poorly defined terminal elimination phase on Day 14. For those groups where a half-life could be measured on Day 14, the $t_{1/2}$ for tenofovir ranged from 11.3 to 16.2 hours. It is possible that continued absorption of tenofovir from the rectal site of administration contributed to the inability to accurately measure half-life on Day 14. Tenofovir plasma concentrations

increased in both female and male rabbits with increasing dose. However, the increase in exposure was somewhat less than dose proportional. On Day 14 when tenofovir plasma concentrations were most consistent across individual animals, the decrease in dose-proportional exposure for C_{max}/Dose between Group 3 (10 mg) and Group 5 (100 mg) was 66% and 18% for female and male rabbits, respectively. The decrease for AUC_{last}/Dose between Group 3 and Group 5 was 52% and 32% for female and male rabbits, respectively. There was a marked increase in tenofovir exposure over the 14 days of rectal administration. Accumulation ratios (AUC_{last} Day 14/AUC_{last} Day 1) varied from 7.2 to 23.7 across dose groups.

The No Observed Adverse Effect Level (NOAEL) for rectal administration of test article in this study was greater than the highest concentration tested, i.e., >10% tenofovir in vaginal gel (a 100 mg dose).

Effectiveness-Vaginal Administration

Six independent nonhuman primate studies provided some degree of evidence for efficacy using vaginally administered 1% or 10% gel (see Table 4).[44] Although these data are limited and a powered statistical determination as to the efficacy of tenofovir 1% gel versus 10% cannot be made, empirical examination of the efficacy data identifies tenofovir 1% gel as the lowest efficacious concentration tested when given within two hours of virus challenge. All studies used SIVmac251, a highly infectious SIV isolate, and Indian-origin rhesus macaques (with the exception of study 6). Study 1 demonstrated protection of all four macaques that received 10% tenofovir gel as compared to no protection in the 2 macaques that received placebo gel. Likewise in study 2, 11 of 15 macaques that received 1% or 10% tenofovir gel were protected as compared to no protection in the 5 untreated control macaques that received no gel product. In studies 3, 4, and 5, <100% of the untreated controls were infected making these data problematic to interpret.

Table 4: Use of Topical Tenofovir to Prevent Vaginal Transmission of SIV

Study*	Number of Exposures	Treatment	Time of Administration	Number Infected	Progesterone Pretreatment
1	2	1 mL vehicle	–24 h, 0 h, 24 h, 48 h	2 of 2	No
		10% tenofovir	–24 h, 0 h, 24 h, 48 h	0 of 4	
2	1	untreated control	N/A	5 of 5	No
		10% tenofovir	–24 h , –15 m, +24 h	1 of 5	
		1% tenofovir	–24 h , –15 m, +24 h	1 of 5	
		1% tenofovir	–15 m	2 of 5	
3	1	untreated control	N/A	2 of 5	No
		vehicle	–15 m	1 of 5	
		1% tenofovir	–15 m	1 of 5	
		1% tenofovir	–2 h	3 of 5	
		1% tenofovir	–8 h	1 of 5	
4	1	untreated control	N/A	4 of 5	No
		vehicle	–15 m	2 of 5	
		1 % tenofovir	–15 m	1 of 5	
		1 % tenofovir	–2 h	1 of 5	
		1 % tenofovir	–8 h	2 of 5	
5	1	untreated control	N/A	2 of 5	No
		vehicle	–2 h	2 of 5	
		1 % tenofovir	–2 h	0 of 5	
6	1	1 % tenofovir	–12 h	5 of 8	Yes
		vehicle	–12 h	8 of 8	
		1 % tenofovir	–24 h	8 of 8	
		vehicle	–24 h	8 of 8	
		untreated control	N/A	8 of 8	
		1 % tenofovir	–72 h, –48 h, –24 h	6 of 8	

* All studies were performed with the SIVmac251 isolate of SIV, and female rhesus macaques were inoculated intravaginally. Virus challenges were performed without progesterone pretreatment in Studies 1–5; macaques in Study 6 were pretreated with 30 mg Dep-Provera 30 days prior to viral challenge. The indicated studies were performed by 3 independent investigators with Studies 2, 3, 4, and 5 being performed by the same laboratory.

Study 6 was different from the first five studies in that Chinese-origin rhesus macaques were used and they were pretreated with progesterone before virus challenge to enhance susceptibility to infection and synchronize reproductive cycles. This study was designed to determine whether topical dosing of tenofovir gel could be disassociated from the coital act while remaining an effective microbicide, in a regimen consistent with the long intracellular half-life of the active metabolite, tenofovir diphosphate. A total of 48 macaques, pretreated with a 30 mg dose of depot medroxyprogesterone acetate (DMPA) 30 days prior to viral challenge, were divided into 6 groups of 8 animals each. Group 1 received one topical vaginal dose of tenofovir 1% gel 12 hours prior to one intravaginal viral challenge with a dilution of SIVmac251 stock representing approximately 50 $TCID_{50}$ (50% tissue culture infective dose). In parallel, Group 2 received matched placebo gel. Group 3 received a single dose of tenofovir 1% gel twenty-four hours prior to viral challenge. The matched placebo gel was administered to Group 4 twenty-four hours prior to viral challenge. Group 5 was an untreated control group receiving only the viral challenge. A single dose of tenofovir 1% gel was administered topically to Group 6 animals at 72, 48, and 24 hours prior to viral challenge. Thus, Group 6 animals received 3 consecutive days of gel; Group 4 served as the placebo control for Group 6. Based on plasma viral load, all untreated control animals became infected as did all placebo gel-treated macaques. Three animals were

protected from infection in Group 1 receiving a single dose of tenofovir 1% gel 12 hrs prior to virus exposure. Although no macaques receiving a single dose of tenofovir 1% gel 24 hours prior to virus exposure were protected, two of eight animals in Group 6 receiving multiple doses of tenofovir 1% gel remained uninfected. Infection status was confirmed using virus co-culture, seroconversion and lymph node deoxyribonucleic acid polymerase chain reaction (DNA PCR). These data show 24 of 24 placebo gel-treated or untreated macaques became infected with SIVmac251 while 5 of 24 macaques were protected from SIV infection by vaginally administered tenofovir 1% gel.

Progesterone pretreatment (30 mg DMPA) is used in macaque studies to increase susceptibility to infection by a mechanism thought to involve thinning of the vaginal epithelium. It is generally required to achieve 100% infection in untreated control animals challenged with less infectious Simian/Human Immunodeficiency Virus (SHIV) chimeric viruses. Although animals were pretreated with DMPA in this study but not the previous studies as shown in Table 4 (studies 1−5), this pretreatment may not be required for such a highly infectious virus as SIVmac251. In view of the potent infectivity of this virus, the lack of an endpoint in the animal titration of this stock[66], and increased susceptibility resulting from progesterone pretreatment, it is possible that the amount of virus used was too high, thereby masking any protective effect. Further studies are required to understand the factors that impact protection by intravaginal tenofovir gel in the macaque model.

Effectiveness-Rectal Administration

The rectal application of tenofovir was evaluated for protective efficacy against rectal challenge with simian immunodeficiency virus (SIV) in a well established and standardized pre-clinical macaque model.[60] A total of 20 purpose-bred Indian rhesus macaques were used to evaluate the protective efficacy of topical tenofovir. Six animals received tenofovir 1% gel *per rectum* 15 minutes prior to virus challenge and 3 macaques received tenofovir 1% gel per rectum 2 hours prior to virus challenge, whereas 4 macaques received placebo gel and 4 macaques remained untreated. In addition, 3 macaques were given tenofovir gel 2 hours after virus challenge. Following intrarectal instillation of 20 median rectal infectious doses (MID_{50}) of a non-cloned, virulent stock of $SIV_{mac251/32H}$ all animals were analyzed for virus infection, by virus isolation (VI) from peripheral blood mononuclear cells (PBMC), quantitative proviral DNA load in PBMC, plasma viral ribonucleic acid (vRNA) load by sensitive quantitative competitive (qc)-RT PCR and presence of SIV-specific serum antibodies by ELISA. A significant protective effect was seen (p=0.003; Fisher's Exact Probability test) wherein 8 of 9 macaques given tenofovir *per rectum* either 15 minutes or 2 hours prior to virus challenge were protected from infection (n=6) or had modified virus outcomes (n=2) while 4 of 4 untreated macaques and 3 of 4 macaques given placebo gel were infected, as were 2 of 3 animals receiving tenofovir gel after challenge. Moreover, analysis of lymphoid tissues *post mortem* failed to reveal sequestration of SIV in the protected animals.

Colorectal explants from non-SIV challenged tenofovir treated macaques were resistant to infection *ex vivo*, whereas no inhibition was seen in explants from the small intestine.

Tissue-specific inhibition of infection was associated with the intracellular detection of tenofovir. In colorectal explants from 3 of 4 animals, complete or nearly complete inhibition of virus replication was seen and in the other animals, a high level of variability between replicate samples resulted in lower mean inhibition. In contrast, inhibition of virus replication was not seen in explants from the small intestine suggesting that tenofovir was, at least in part, acting on cells at the virus portal of entry.

Analysis of plasma tenofovir concentration at the time of virus challenge, 15 minutes after gel administration, revealed a strong positive association with protective efficacy. The lowest concentration of plasma tenofovir associated with protection was 119.9 ng/mL. Taking into account estimated plasma volume, protection was associated with as little as 0.11% of the total tenofovir applied; however, this is systemic exposure, rather than local exposure. Moreover, an effect upon plasma viremia was observed with as little as 0.06% of applied tenofovir detected in plasma at 15 minutes. In animals given tenofovir 2 hours prior to virus challenge, plasma tenofovir concentrations at the time of challenge ranged between below the 10 ng/mL limit of detection to 23.3 ng/mL. These results therefore suggest that drug concentration peaks rapidly after rectal dosing. Interestingly ileum/jejunum tissue taken from dosed macaques remained susceptible to infection, and was confirmed by the lack of detectable drug in these tissues. This suggests that secondary distribution to this site is insignificant and supports the importance of comparing an oral, systemically-delivered dose to a topical, locally-delivered dose.

2.8.2 2% Nonoxynol-9 Gel

Toxicology-Vaginal Administration

Galen and colleagues[67] conducted the first study to evaluate the murine mucosal response to repeated microbicide applications. Female BALB/c mice were pre-treated with a 2 mg subcutaneous dose of medroxyprogesterone acetate 5 days prior to a 14-day, once daily, 40 µL, intravaginal dose of Advantage-S (3.5% N-9, Columbia Laboratories Inc., Livingston, NJ), 2% PRO 2000 Gel (Indevus Pharmaceuticals Inc., Lexington, MA) or HEC gel (supplied by the International Partnership for Microbicides). On Day 7, untreated and HEC-treated mice showed no histological changes whereas mice in the N-9 group showed epithelial disruption with some necrosis, and the mice in the PRO 2000 group showed scattered neutrophils but no evidence of epithelial damage or necrosis. The presence of N-9 also resulted in an increase in proinflammatory cytokines and chemokines and a significant increase in transcriptional activators NF-κB and AP-1, relative to the placebo gel. To determine if the noted damage resulted in the likelihood of increased risk to infection, mice were challenged with a sub-lethal dose of herpes simplex virus type 2 (HSV-2), 12 hours following their seventh intravaginal dose of gel. Mice in the N-9 group displayed a significant increase in susceptibility to HSV-2 as compared to the mice in the PRO 2000 and placebo groups. Collectively, these data support the clinical findings that N-9 induces sustained damage resulting in increased susceptibility to infection with HSV in this case.

The effects of repeated applications of two commercially available intravaginal spermicides were evaluated in a monkey model.[68] Effects of Conceptrol® (4% N-9; Ortho Pharmaceutical Corp, Raritan, NJ), benazalkonium chloride (1.2%; Stepan & Co, Northfield, IL), and a 1:1 combination of both products, were evaluated on the vaginal microflora and lower reproductive tract tissues in 14 female pig-tailed macaques. The monkeys received daily vaginal applications (1.5 mL) of either N-9 (n=4), benazalkonium chloride (n=5), or a combination of both products (n=5) for 3 to 4 days. The vaginal wall and cervix were observed by modified colposcopy and a vaginal swab for microbial assessment was taken prior to application of study product. The vaginal swab was repeated 30 minutes after application of study product. Cervical biopsy specimens were also collected in a subset of monkeys. Monkeys in the N-9 arm were treated daily for 3 days, followed by a 2 day resting period, and then treated daily for an additional 3 days. The monkeys in the benazalkonium chloride and the combination arms were treated daily for 4 days.

Colposcopic findings showed evidence of cervical erythema (n=4) and cervical papillae (n=3), and vaginal erythema (n=4) after repeated applications of N-9. Epthilelial disruption, however, was not noted in any of the monkeys in the N-9 arm, but was noted in the monkeys in the benazalkonium chloride arm (n=5) and in the combination arm (n=5).

Toxicology-Rectal Administration

Given the similarities between the rectal flora and epithelial tissue of the pig-tailed macaque (*Macaca nemestrina*) and humans, Patton and colleagues assessed the effects of repeated applications of Conceptrol® (Advanced Care Products, Skillman, NJ, USA) containing 4% N-9 on the microflora and rectal epithelium in a macaque model.[47] The macaques were randomized to one of three groups: Conceptrol®, placebo gel, and no product (8 per group). Macaques in the Conceptrol® and placebo gel groups received daily applications of the study products at 24-hour intervals, for 3 days. Rectal pH swabs, microbiology samples, and rectal lavage specimens were collected from all macaques prior to each application of study product, and again at 15 minutes post-insertion. Final samples were collected on Day 4. The findings showed that repeated applications of Conceptrol® resulted in a reduction of H_20_2-producing microorganisms and decreased detection of black pigmented anaerobic gram negative rods. Furthermore, sheets of epithelium and epithelial cells were observed in the lavage specimens 15 minutes post-insertion of Conceptrol®, and not for the placebo gel and no product groups. The presence of sheets of epithelium in the lavage specimens significantly increased with each successive application of the N-9 containing product. The N-9 product also caused red blood cells to be observed in the lavage specimens. This study points to the imperative need to conduct animal studies to assess the safety and efficacy of microbicides applied rectally, since it is likely that these products will be used rectally regardless of indication for vaginal use, once such a product is approved.

A study assessing the safety of several commercially available sexual lubricants including K-Y® Plus containing 2% N-9 (positive control) as well as phosphate buffered saline (PBS-negative control) and Carraguard, an investigational product from the Population Council, was conducted in 6 to 8 week old BALB/c mice (Charles River,

Wilmington, MA).[69] Cytotoxicity, rectal HSV-2 enhancement, and rectal sloughing assays were performed to assess the effects of the study products on the rectal epithelium. Out of the products used in this study, K-Y Plus was shown to have both the greatest anti-HIV activity and simultaneously cause the greatest amount of disruption to the rectal epithelium.

Effectiveness-Vaginal Administration

In a study by Miller et al.,[70] two different preparations of nonoxynol-9, were found to prevent the genital transmission of SIV (cell-free SIV suspension; 10^4 IV animal infectious dose) among rhesus macaques (colony-bred, > 5 years of age). As little as one mL of nonoxynol-9 contraceptive foam (12.5% vol/vol), administered intravaginally, was enough to prevent transmission in three of the six animals exposed and tested, and, intravaginal administration of as little as one mL of nonoxynol-9 contraceptive gel (3% by weight) prevented the genital transmission of SIV in two of six animals exposed and tested. No striking differences existed in the level of protection provided by either gel or foam preparations, but it is evident that the active ingredient in both was capable of providing some level of protection against genital transmission of SIV.

2.8.3 Placebo Gel

HEC is the thickener in the placebo gel. The results of multiple animal studies (vaginally administered product) have been consistent with the safety of this ingredient.[48] A recently completed rectal study in a macaque model also appears to be consistent with the safety of this ingredient.[71]

Toxicology

Up to 55 IV 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.[72] 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. 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).

Intraperitoneal administration of unformulated HEC to pregnant mice in a 1% and 4% concentration caused an increase in resorption, but no detectable increase in birth defects.[73] 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.[74]

CF-1 mice (number not specified) pretreated with medroxyprogesterone acetate were administered 0.02 mL of HEC gel vaginally, followed by a 0.01 mL inoculum of 10 intravaginal $dose_{50}$ units of HSV-2 0.3 minutes later.[57] 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. Control animals were treated

similarly but were not administered the test article. Infection rate following pretreatment with HEC gel (90%) was not significantly different from pretreatment with PBS (80%) or from mice given no treatment (% not specified). HEC gel did not enhance susceptibility of mice to HSV-2 when administered 12 hours before vaginal challenge.[48]

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.[48] 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. Histopathological 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.

HEC gel was used as the placebo comparator in a recent rectal safety study of a combination microbicide in a macaque model.[71, 75] A third study arm received no product and served as a negative control. Rectal safety of the active product and HEC gel was evaluated following four daily applications of study products. Rectal flora, pH, and rectal lavage samples were assessed pre- and post-dosing and showed no evidence of toxicity in the macaques that received HEC gel. The infrequent evidence of epithelial sloughing and rare incidence of associated blood cells in rectal lavage samples was similar in the HEC gel and no product arms of this study.

The effect of HEC gel on vaginal transmission of $SHIV_{162p3}$ (10^3 $TCID_{50}$) to rhesus macaques was determined in two separate studies (n = 5, n = 3, respectively).[48] 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 ribonucleic acid (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 macaques were infected, as determined by the presence of viral RNA in circulating blood, regardless of the pH of the formulation.

2.9 Human Clinical Studies

2.9.1 Tenofovir 1% Gel

RMP-02/MTN-006 and MTN-007 will be the first rectal safety studies of tenofovir 1% gel. However, a broad range of reproductive tract studies have been completed, or are ongoing and these data are summarized below.

Pharmacokinetics

Data from "Phase 1 Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel", also known as HPTN 050 has been recently published.[76] Eighty-four (60 HIV negative and 24 HIV positive) women applied either 0.3% or tenofovir 1% gel once or twice daily for 14 days. Systemic absorption was limited (maximum serum levels 3.1-25.8 ng/mL).

In MTN-002, the first microbicide trial to be conducted during pregnancy, 16 women received a single vaginal dose of tenofovir 1% gel prior to elective cesarean section. Tenofovir levels were measured in blood, amniotic fluid, cord blood, endometrial tissue, and placental tissue. Plasma tenofovir levels were compared to historical controls. Study results demonstrated that the PK levels of a single vaginal dose of tenofovir 1% gel in pregnant women was similar to those found in non-pregnant women and that serum tenofovir levels were up to 50 – 100 times less as compared to standard oral dosing.[77] Additionally, tenofovir was shown to get to the fetal compartment with low overall cord levels (~40 times less than oral dosing), but with a similar cord blood: maternal ratio. Overall findings suggest that tenofovir is safe for use in term pregnancy and warrants additional investigation during pregnancy.

Safety

In HPTN 050, the tenofovir 1% gel formulation was well tolerated in both HIV-uninfected and -infected women.[76] Further, 94% of female participants and 81% of male participants indicated they would definitely or probably use tenofovir gel in the future. While a number of participants (92%) reported some type of adverse event (AE), the majority of them were mild (87%) and limited to pruritus (n = 18), erythema (n=14), petechiae/ecchymosis (n = 14), vaginal discharge (n = 13), and burning (n = 10). Only four severe AEs were reported, but of these, only one (lower abdominal pain) was thought to be product-related. Product concentration, sexual activity and HIV status were not associated with a specific AE pattern. No clinically significant systemic toxicity was observed. No serious adverse events (SAEs) were reported.

In a male tolerance study (CONRAD A04-099/IND 73,382), tenofovir 1% gel was well tolerated in men following seven days of once daily exposure, for 6 to 10 hours, to the penis. There were few reported and observed genital findings after product use including mild pain (burning, irritation, discomfort) and pruritis.[44] All observed findings were classified as mild, small in size and requiring no treatment. Reported symptoms were mild, of short duration and resolved by the final visit. There were no noticeable differences between signs and symptoms of genital irritation in the circumcised compared to uncircumcised group.[44, 78]

A Phase 2 study of tenofovir 1% gel (HPTN 059) has completed follow up. This study assessed safety and acceptability of, and adherence to a regimen of tenofovir gel for vaginal use in HIV-uninfected women versus a placebo gel. Exploratory objectives included measurement of vaginal flora characteristics, assessment of the effects of gel on genital cytokine and chemokine expression, and the evaluation of cytokine and chemokine expression to correlate expression with evidence of inflammation, epithelial

disruption and genital symptoms. The study was a four-arm, three-site, randomized, controlled trial comparing gel used once daily and gel used prior to intercourse, to placebo gel, with 6 months gel exposure and follow-up. The study was conducted among 200 women in Pune, India; Birmingham, Alabama, USA; and New York, New York, USA. Participants were sexually active, HIV-uninfected women between ages 18 and 50, but not menopausal or post menopausal. Participants had six months of study gel exposure and follow-up. They were randomized to either once daily or coitally dependent group, and received either tenofovir or placebo gel. Participants received single use unit dose tubes and single-use applicators.

No statistically significant differences were seen between those receiving active and placebo gels in complete blood count (CBC), liver function tests, or renal function tests. Among those using a study gel daily, no participants had pelvic exam findings involving generalized erythema or severe edema or deep epithelial disruption at any follow-up visit during the study. At the Week-24 Visit, no participants had exam findings suggestive of vaginitis, cervicitis, superficial disruption, disrupted blood vessels, or intermenstrual bleeding. Adherence to study gel was high, and was supported by PK data. 79% of women reporting gel use in past 12 hrs had low but detectable plasma tenofovir supporting self-reported adherence data. Daily and coital use was highly acceptable to women. These data suggest a favorable safety and acceptability profile of tenofovir gel, and support routine monitoring for genital findings among women without genital symptoms at six month intervals.[79]

A Phase 2b study of vaginally-administered tenofovir 1% gel use (CAPRISA 004) has recently completed follow-up and data analysis.[80] This study, conducted among sexually active, HIV-uninfected women at an urban and rural site in South Africa, compared the safety and effectiveness of tenofovir 1% gel when use within 12-hours before and after intercourse, versus placebo gel (HEC). Safety assessments as well as HIV and urine pregnancy tests were performed at monthly follow-up visits. Pelvic exams were also performed at quarterly visits.

Study results suggest that vaginally-administered, coitally-dependent use of tenofovir 1% gel is safe. No increases in renal, hepatic, pregnancy-related, or genital AEs were observed. Additionally, tenofovir 1% gel was shown to reduce HIV infection by approximately 39% regardless of sexual behavior, condom use, HSV-2 infection, or urban/rural location. It is important to note, however, that the high acceptability rate (~97%) did not correspond to the average adherence rate (~61%). While these data suggest a favorable safety and effectiveness profile for tenofovir 1% gel, further studies must be done to assess whether more frequent (e.g. daily) dosing will enhance adherence and as a result, effectiveness, without compromising participant safety, and whether tenofovir 1% gel is safe, well-tolerated, and efficacious when administered rectally.

Drug Resistance

In HPTN 050, no new resistance mutations evolved in plasma or cervicovaginal lavage after 14 days of tenofovir gel use, but 3 women had plasma mutations associated with

low level tenofovir resistance identified at both Day 0 and Day 14 (M41L, L210M, ±T215I/Y).[76]

Other Studies of Tenofovir for HIV Prevention

Several other studies of the safety and/or effectiveness of topical tenofovir 1% gel as an HIV prevention strategy are summarized below in Table 5.

Table 5: Other Studies of Tenofovir 1% Gel

Location	Sponsor	Population	Design
USA, Dominican Republic	CONRAD A04-095/IND 73,382	Sexually abstinent women	PK study; single dose and 14-day once or twice-daily.
South Africa, Uganda, USA	DAIDS/MTN-001/IND 55,690	Sexually active women	Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir
USA	DAIDS IPCP/RMP-02/MTN-006/CONRAD IND 73,382	Sexually abstinent (for active phases of study and for 5 days following biopsy collection) women and men	Phase 1 Rectal PK and Acceptability

Studies examining the safety and/or effectiveness of oral formulations of tenofovir as a prevention strategy are summarized in Table 6 below.

Table 6: PrEP Studies

Location	Sponsor	Population	PrEP Strategy
Phase 2			
West Africa (Ghana, Nigeria, Cameroon)	Family Health International	936 high-risk women	TDF
United States	Centers for Disease Control and Prevention (CDC)	400 men who have sex with men	TDF
Phase 3			
Thailand	CDC	2,000 injection drug users (~20% women)	TDF
Botswana	CDC	1,200 men and women	FTC/TDF
Peru, Ecuador, Brazil, Thailand, South Africa, United States	NIH (iPrEx Study, IND 71,859)	1,400 men who have sex with men (potential expanded sample size of 3,500)	FTC/TDF
Africa	Family Health International	3,800 high-risk women	FTC/TDF
Africa	University of Washington, Gates Foundation	3,900 HIV-1 seronegative partners within HIV-1 discordant couples	FTC/TDF TDF

2.9.2 2% Nonoxynol-9 Gel

Safety-Vaginal Administration

To better understand the molecular basis of N-9 induced inflammation, Fichorova and colleagues[81] evaluated 10 healthy white females at low-risk for HIV infection after single or multiple doses of N-9. Two protocols were used. The first included a single intravaginal dose of 150 mg N-9, while the second included 3 intravaginal doses of 150 mg N-9. Cervicovaginal lavages (CVL) were sampled before and at 12, 36, and 60 hours following administration. CVL was clarified by pelleting the cells and the supernatant was portioned into aliquots and frozen. CVL supernatant was tested for expression of several cytokines and secretory leukocyte protease inhibitor (SLPI) and neutrophil elastase (NE). The cell pellet was suspended in 1 mL PBS and tested for polymorphonuclear cells and the remainder of the cells were placed on a slide to stain for immune cells and a central inflammatory protein, NF-κB, by immunohistochemistry. While a single dose showed modest increases in cytokine levels, multiple doses of N-9 significantly elevated levels of IL-1α, IL-1β, and NE while significantly decreasing SLPI levels as compared to baseline samples. Collectively these data suggest that repeat exposure to N-9 increases the inflammatory response in the female genital tract which has important implications for HIV acquisition.

The vaginal safety of three different concentrations of C31G was assessed in a Phase 1, randomized, double-blind, dose-escalation study.[82] C31G is a surfactant and was under investigation as a possible microbicide and contraceptive. Extra strength (ES) Gynol II® (3% N-9) was used as a comparator since studies have shown that frequent doses of N-9 damage the vaginal epithelium.[83]

A total of sixty-four, low-risk women were randomized to either different concentrations (0.5%, 1.0%, 1.7%) of C31G or to ES Gynol II®. Participants were instructed to apply the study gel once daily for seven consecutive days. If after the first seven days of use, the products appeared safe, participants were asked to apply the study gel twice-daily for seven consecutive days. Safety was assessed by symptomatic irritation, naked eye, and colposcopy. Results of the study showed that the lower concentrations of C31G were less irritating than either the 1.7% C31G or ES Gynol II®. Participants in the Gynol II® arm experienced the most irritation over the course of both treatment periods (87% and 93% respectively) and also accounted for the largest proportion of product -related and non-mild events.

N-9 (Conceptrol®) was also used as the positive control in a Phase 1 safety and colposcopy study of polystyrene sulfonate (PSS) gel conducted by Mauck and colleagues. A total of forty-eight women were randomized to apply 2.5 mL of PSS vehicle, 5% PSS (125 mg), 10% PSS (250 mg), or Conceptrol® (100 mg N-9), once daily for six consecutive days. The primary safety outcome was the proportion of participants who experienced any signs (epithelial changes) or symptoms of genital irritation (itching, pain, and abnormal bleeding). Participants in the Conceptrol® group experienced more signs and symptoms of genital irritation than their counterparts in the PSS group.

In a study designed to evaluate the safety of nonoxynol-9 on the genital mucosa of women from three centers in Malawi and Zimbabwe in preparation for a planned Phase 3 trial of effectiveness of N-9 as a microbicide in lowering the risk of acquiring HIV, 180 women were enrolled and randomized to either N-9 or placebo gel.[84] The women were to insert the gel into the vagina twice daily for 14 days, and returned for examination on days 7 and 14.

The total number of adverse events in the N-9 group was statistically significantly higher than in the placebo group (40% versus 13%, P<0.01). There was a difference in the number of reported symptoms between the two groups, with 38% in the N-9 group and 13% in the placebo group, with the specific symptoms of genital itching being reported more often in the N-9 group as compared with placebo (19% versus 8%, respectively). During the pelvic examinations at the two follow-up visits, erythema was found in 14/89 (16%) of the women on N-9, but only in 2/90 (2%) of the women on placebo. When evaluating epithelial disruptions found at follow-up, no increase in the number of genital ulcers was identified (2% versus 1%), however, there was an increase in lesions other than ulcers (13% versus 3%), and in epithelial sloughing (7% versus 0). Although this study found an increase in the rate of adverse events in the group using 100 mg of N-9 twice daily as compared with the placebo group, it was thought that these were not sufficient to cancel the planned Phase 3 effectiveness study. However, the Phase 3 study was canceled when the investigators considered the negative results from the COL-1492 effectiveness trial[85] which evaluated the use of 52.5 mg N-9, along with these safety results.

In 1998, results were published from a large multicenter randomized trial designed to determine the safety of COL-1492, a spermicidal gel that contains 52.5 mg nonoxynol-9 per dose.[83] The design of the study included both a placebo gel arm and a no-gel control arm, in addition to the active agent arm. Participants randomized to either the placebo or COL-1492 arm were asked to use the gel once daily for 14 consecutive days. Physicians and participants were blinded to study product. Clinical evaluations for patients in all three treatment groups were scheduled at days 0, 7, and 14, at which time a history was obtained and a colposcopy was performed. Additionally, participants were requested to have an evaluation if they experienced any health problems between scheduled visits. Outcomes included reported genital symptoms, incidence of gynecological signs and genital lesions revealed by colposcopy.

For the 534 women enrolled and followed in the study, the incidence of genital symptoms was significantly greater in the COL-1492 group than in the placebo or control group. Women on COL-1492 were also significantly more likely to develop a lesion than women in the other groups (P<0.001), with petechial hemorrhage being the most commonly reported abnormality (20.1% in the COL-1492 group vs. 9% in the placebo group vs. 7.3% in the control group). The incidence of ulceration and abrasion was low overall (1-3%) and was not statistically significantly different among the three groups. Interestingly, when comparing colposcopy results for the placebo gel group with the no treatment control group, the only significant difference found was a higher incidence of edema in the placebo group. There was also a higher incidence of

reported symptoms (particularly vaginal discharge and genital itching), which may be partially due to leakage of the product out of the vagina.

The effect of nonoxynol-9 (N-9) on the female genital tract was examined in a randomized double-blind safety study by Stafford, Ward, Flanagan, et al.[86] In this study, forty female volunteers were randomized to receive either N-9 at a concentration level of 20 mg/mL (100 mg/dose) or a placebo gel. Participants were asked to insert 5 mL of gel on each of 7 consecutive nights, and were examined by a physician at the screening visit, on Day 0 (entry), Day 7 (post gel) and Day 14 (final visit).

This study found that N-9, given in a standard spermicidal dose for 7 consecutive days, was associated with increased symptoms of irritation (50% in the N-9 group vs. 25% in the placebo group) as well as colposcopic evidence of erythema (45% vs. 10 %) and histological evidence of inflammation in the genital tract (35% vs. 10%). Additionally, a temporary reduction in numbers of lactobacilli isolated was seen more frequently in the women using N-9 gel. The inflammatory and microbiologic adverse events found in the women using the placebo gel were thought to be due to the presence of biologically active agents used as preservatives in the placebo gel. The differences in adverse events between the two groups were not statistically significant, likely due to the small sample size. The increase in N-9 induced damage and irritation to the female genital tract as highlighted above, underscores the rationale for inclusion of N-9 as the positive control in MTN-007.

Safety-Rectal Administration

A study conducted by Tabet et al., showed no clinical evidence of rectal or penile disruption or inflammation resulting from 3.5% N-9 use in escalating doses up to 6 weeks.[14] Tabet and colleagues conducted an open-label, Phase 1 study evaluating the safety and toxicity of Advantage 24 (Columbia Research Laboratories, Inc., Rockville Centre, New York, NY) containing, 52.5 mg of N-9 in 1.5g of gel, to rectal and urethral mucosa and penile epithelium in HIV-concordant, monogamous, male couples.

Participants were instructed to apply the N-9 or placebo gel once or twice daily and to have anal sex at least three times a week, within 30 minutes of product application. All participants used the placebo gel for one week, and then used the N-9 gel in escalating doses (up to two applicators twice daily) for 6 weeks. Anoscopies were done after 2, 5, and 6 weeks of N-9 use and rectal biopsy specimens were collected after 5 and 6 weeks of N-9 use for all receptive partners. Low-dose N-9 was not associated with clinical rectal and penile disruption or inflammation, although observations of histological abnormalities were common during use of both the N-9 and placebo gel. It was not clear whether the histological abnormalities were associated with use of the active product, other product components or anal sex. Results of this study were in contrast to other rectal studies discussed below where samples are collected shortly after product application.

Following up on a study that demonstrated enhanced HSV-2 acquisition in mice as a result of rectal application of N-9, Phillips et al., examined rectal lavage samples from 4 participants following rectal application of N-9.[13] K-Y® Plus (Ortho-McNeil

Pharmaceutical, Raritan, NJ) containing 2% N-9, Forplay® (Trimensa Pharmaceuticals, Newbury Park, CA) containing 1% N-9, PC-515 with carrageenan (FMC, Rockland, ME), and methyl cellulose (Mallinckrodt, Paris, KY) were used in this study. In addition to the baseline rectal lavage sample, participants were ask to rectally apply each of the four product formulations followed by rectal lavage at 15 minutes and 8-10 hrs post-insertion, with a minimum of 72 hours between each application and lavage. K-Y® Plus was shown to have caused the greatest amount of epithelial exfoliation, with sheets of epithelium evident in all four lavage specimens, whereas only two of the lavage specimens from Forplay® showed evidence of epithelial exfoliation, although to a much lesser extent than that from use of K-Y® Plus.

Building on a study that assessed the impact of N-9 on the rectal epithelium, Phillips et al.[13] conducted another study of N-9 in 18 participants that included rectal biopsies and rectal lavage. K-Y® Plus (Ortho-McNeil Pharmaceuticals, Raritan, NJ), containing 2% N-9 was the study product, since previous studies[12] have shown it to cause epithelial sloughing at 5 mL. Specimens (via lavage and biopsy) were collected at baseline and again at 15 minutes, 2 hrs, and 8 to 12 hrs after insertion (lavage only). No materials were observed in the baseline collection, but sheets of gut epithelium composed of columnar and goblet cells were observed at 15 minutes after insertion. Significantly fewer materials (degraded cells and bacteria) were observed at the 2 hour time point, and no cellular materials were observed at the 8 hour time point. Results from this study suggest that exfoliation and repair of the rectal epithelium occur within a two hour period.

Thus it appears that rectal administration of N-9 results in mild, but transient epithelial disruption. To capture those events, it is critically dependent on sampling time following application. This information has guided the design of the first rectal microbicide safety study using the vaginal formulation of UC781 as well as the current protocol using the vaginal formulation of tenofovir 1% gel.

Effectiveness-Vaginal Administration

Van Damme and colleagues[85] evaluated the effectiveness of COL-1492 gel (52.5 mg N-9, Columbia Laboratories, New York, NY USA) in a randomized, placebo-controlled, triple-blinded, phase 2/3 trial with a total of 892 female sex workers in Benin, the Ivory Coast, South Africa, and Thailand. Of the 795 women included in the analysis, 376 were randomized to the N-9 arm and 389 to the placebo arm (Replens, Columbia Laboratories, Paris, France). Women were instructed to apply the gel for vaginal intercourse (and again if they had cleaned their vagina after the last act of intercourse). On average, women reported using more than 3.5 applicators per day. It was noted that the risk for HIV acquisition was twice as high for women in the N-9 group as compared to those in the placebo group. The risk for HIV acquisition, however, did not differ among women who reported using the gel less frequently than 3.5 times per day. The results from this study demonstrated that frequent (> 3.5 times/day) N-9 use induced damage to the vaginal epithelium, which resulted in a great risk for acquisition of HIV.

2.9.3 Placebo Gel

Unformulated hydroxyethylcellulose is known to be a non-irritating substance in humans (skin sensitization is unusual), with doses less than 2 g/kg by ingestion not expected to be toxic.[87] 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.

Safety-Vaginal Administration

The hydroxyethyl cellulose-based placebo formulation was developed and adopted for use in the HPTN 035 microbicide study, the Phase 2/2B 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 Phase 1 study of daily vaginal HEC gel exposure was conducted in 2003.[88] 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: 1) 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 2) 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 group 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 than in the PSS group. Three out of 14 women in the HEC group (21.4%) had colposcopic findings that included erythema, petechiae and peeling.[88] However, 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.

Safety-Rectal Administration

A 2-period crossover study of commercially available lubricant gels, by Fuchs and colleagues[89] demonstrated that osmolar properties affected epithelial denudation and product absorption. The gels were made into isosmolar and hyperosmolar mixtures and compounded with a radio-isotope label to address product absorption. Ten healthy male subjects (all MSMs) including 8 seropositive and 2 seronegative men were recruited for the study. All subjects received a 10 mL rectal dose of hyperosmolar ID Glide (Westridge Laboratories, Inc., Santa Ana, CA); 3429 mOsm/kg [pH 4.79]) and a 10 mL rectal dose of an isosmolar preparation of FemGlide (Cooper Surgical Inc., Trumbull, CT)/ID Glide combination gel (283 mOsm/kg [pH 6.77]). Sigmoidoscopy was

performed within 1.5 hours of dosing, with cytobrush sampling at 10 cm and cytobrush and biopsy sampling at 12.5 cm (referred to as 10 cm in results), 40 cm, and 42.5 cm (referred to as 40 cm in results). A paired comparison showed a statistically significant difference in gel concentration between the isosmolar and hyperosmolar products at 10 cm. The median isotope concentration in the isosmolar gel arm was greater at 10 cm than at 40 cm, whereas there was no significant difference at 10 cm and 40 cm in the hyperosmolar gel arm indicating the hyperosmolar gel induced a luminal influx of liquids. The hyperosmolar gel resulted in Grade 3 denudation of the rectal epithelium at 10 cm while the isosmolar gel showed no histological damage. No difference in epithelial structure was observed at 40 cm with either gel. Overall, the results showed epithelial injury is greatest at the site of initial and most concentrated gel exposure which causes mucosal fluid secretion and a dilution of intraluminal gel concentration. While no conclusion could be drawn regarding the timing of repair of epithelial changes in this study, the authors noted that other researchers have reported observations of repair as soon as 2 hours after injury and a resumption to baseline histology at 8 h after insult, prompting the encouragement of future investigation into time-related response, as will be done in MTN-007.

2.10 Justification of No Treatment Arm

MTN-007 will contain three product arms; tenofovir gel, placebo gel, and a 2% N-9 arm. The study will also include a no treatment arm in which mucosal samples will be collected at the same time intervals as the treatment arms; at the Enrollment/Baseline Evaluation Visit, at the Treatment 1 Visit, and at the Final Visit. The purpose of the no treatment arm is to provide data on the baseline levels of the mucosal safety parameters evaluated in the treatment arms. It is acknowledged that the presence of pre-treatment baseline samples for the treatment arms will also provide important comparative data. However, the three evaluations obtained from each participant in the no treatment arm will provide critical data on the biological variability of the mucosal safety parameters. Similar data was generated in the HPTN 056 study where 16 men underwent serial sigmoidoscopy with collection of mucosal samples. However, the HPTN 056 data set is limited as only 4 of the 16 men were HIV negative with a history of receptive anal intercourse. The no treatment control arm may inform identification of any mucosal damage pathways that are not activated by the N-9 arm of the study. Finally, the presence of a no treatment control arm will provide important comparative data with the placebo arm and help determine whether the HEC-based placebo gel is an appropriate control product for future rectal safety studies.

2.11 Study Hypothesis and Rationale

2.11.1 Study Hypothesis

MTN-007 hypothesizes that eight rectal applications of tenofovir 1% gel will be safe, well-tolerated, and acceptable among healthy RAI-abstinent men and women.

2.11.2 Rationale for Rectal Safety Studies

Recently, behavioral publications have emphasized that heterosexual women practice receptive anal intercourse (RAI).[2, 74, 90, 91] Consequently, any vaginal microbicide may well be used in the rectal compartment in association with RAI. Unlike the stratified squamous non-keratinizing epithelium of the vagina, the rectum is lined with a single cell columnar epithelium and represents a biologically distinct compartment for which site specific safety parameters will need to be determined. Developing a rectal safety profile for tenofovir 1% gel vaginal microbicide is an important step in defining the overall safety profile of this product. In addition, successful demonstration of safe and acceptable use of the tenofovir 1% gel formulation rectally may lead to further clinical development of tenofovir 1% gel for rectal use.

There is a well established pathway for the non-clinical and clinical development of vaginal microbicides.[92, 93] Candidate vaginal microbicide products have been evaluated in Phase 1 through Phase 3 studies.[94] To proceed to efficacy studies, candidate microbicides have to pass through a rigorous Phase 1 safety evaluation that routinely includes detailed clinical and colposcopic assessment of the genital compartment. However, no such pathway exists for evaluating the rectal safety of microbicide candidates.

There is relative paucity of safety data for candidate rectal microbicides compared to the vaginal literature. Most studies to date have focused on the surfactant N-9. Initial murine studies showed sloughing of rectal mucosa following application of N-9.[95] Non-human primate studies corroborated this finding and showed sheets of rectal epithelium following a rectal lavage taken 15 minutes after an application of N-9.[47] Human studies followed with similar findings when lavage was performed rapidly after an application of N-9[12, 13]. However, in a rectal safety study that involved daily applications of 3.5% N-9 for 6 weeks, gross mucosal abnormalities were not visualized although mild histological changes on rectal biopsy were reported in 89% of the N-9 group compared to 69% of the placebo arm.[14] These studies set the paradigm for future rectal safety studies as they demonstrated that microbicides that appear safe in the vaginal compartment cannot be assumed to be safe in the rectal compartment.

Histology is preferable to visual inspection which is a coarse measurement of mucosal health for several reasons: 1) the wide spectrum of normal mucosal appearance, 2) inter-observer variability, 3) intra-observer variability.[24] The single-cell rectal lining is easily damaged and quickly repairs. Presence of epithelial cells is normal; mucosal redness, flushing, loss of vascular pattern and even small erosions may all be normal variants and/or a result of colonic preparations. Should any significant abnormalities be noted during the exam, they will be recorded as AEs.

The recently completed UC781 Phase 1 rectal safety study included a broad range of mucosal safety endpoints including: histology, rectal lavage, mucosal cytokines, mucosal T cell phenotype, and fecal calprotectin. Preliminary assessment of the mucosal safety data did not reveal any significant changes associated with product use

(Peter Anton MD, personal communication). These data could be interpreted to suggest that UC781 has a benign safety profile (which may well be true) or that the safety biomarkers used, lacked the sensitivity to identify product-induced mucosal damage. To address this issue, MTN-007 will have a product arm (tenofovir 1% gel), a negative control (placebo gel), and a positive control (2% N-9 gel). All participants will be RAI abstinent for the duration of the study and will receive counseling about the capacity of N-9 to induce mild epithelial disruption.

The rationale for inclusion of an N-9 arm is that we do not have data on the performance characteristics of the immunological biomarkers in the setting of proven inflammation. A recent study has demonstrated the stability of mucosal cytokine and T-cell phenotype in intestinal tissue[11] but did not address changes associated with mucosal inflammation. It is anticipated that MTN-007 participants who are randomized to receive N-9 will experience mild and transient mucosal inflammation that is known to subside within hours of stopping product administration.[12] If the biomarkers in MTN-007 do not increase following administration of N-9, their utility in future microbicide safety studies cannot be recommended. More optimistically, if N-9 associated changes in biomarkers do occur this will be a critical step forward in the development of optimal methods to assess rectal safety of future candidate microbicides.

2.11.3 Rationale for mucosal assays

Repetitive administration of a candidate microbicide to the rectal compartment might result in induction of local immune responses (upregulation of pro-inflammatory cytokines, recruitment of target cells, and/or increased activation of local T-cells), a phenomenon that could be described as mucosal immunotoxicity. Such immunotoxicity could be associated with increased susceptibility to HIV acquisition in sexually active individuals practicing unprotected RAI. As a consequence, MTN-007 has an exploratory objective of determining whether rectal use of tenofovir 1% gel is associated with changes in a broad range of mucosal endpoints.

These endpoints are exploratory but have been previously evaluated in an observational study[11] and in a subsequent rectal safety study of UC781.[15] As previously discussed, repeated rectal administration of UC781 did not result in significant changes in the mucosal parameters that will be evaluated in MTN-007 (Peter Anton MD, personal communication). This finding could be explained by accepting that UC781 has a good rectal safety profile or concluding that the mucosal parameters lacked the sensitivity to identify subtle, but potentially significant, changes in the rectal mucosa. The inclusion of a positive control arm (2% N-9) in MTN-007 is designed to resolve this question.

2.12 Justification of Dosing

MTN-007 is a Phase 1 rectal safety study of the vaginal formulation of tenofovir 1% gel. As a consequence, we have chosen to use the HTI vaginal applicator (HTI Plastics, Lincoln, NE) used in previous vaginal tenofovir gel studies. The primary rationale for

this decision is that until a rectal specific formulation of tenofovir is developed, the only product (and volume of tenofovir gel) available will be the vaginal product.

Choice of the tenofovir 1% vaginal gel concentration is based on both animal and clinical evidence suggesting an appropriate safety profile and potency. Animal and human studies have demonstrated minimal vaginal irritation at this concentration. A rabbit vaginal irritation test identified tenofovir 1% gel as being histopathologically identical to sham or control treatment, while on a qualitative basis 3% gel was more irritating to vaginal epithelia.[44] The tolerability of the 1% gel was confirmed in the HPTN 050 Phase 1 study, the Phase 1 dose ranging study of tenofovir gel (0.3% once daily, then 1.0% once daily, then 0.3% twice daily followed by 1% twice daily).[44, 53, 76] In this study, of the two doses and frequencies studied in the dose finding cohort, the 1% gel applied intravaginally twice daily for 14 days was well-tolerated and was identified as the highest practical dose and frequency for further study in subsequent cohorts.

The second line of evidence is from vaginal transmission inhibition studies performed in nonhuman primates.[44] Six separate studies provided evidence for efficacy of the gel over a range of tenofovir concentrations of 1% to 10%. Although the total data are limited and a powered statistical determination as to the efficacy of tenofovir 1% gel versus 0.3% and 10% cannot be made, empirical examination of the efficacy data identifies tenofovir 1% gel as the lowest efficacious concentration tested when given within two hours of infection. In studies of rectal administration to macaques, 6 of 9 animals given PMPA prior to challenge were protected from overt infection, and virus detection was intermittent or delayed in 2 other macaques. In 4 of 4 untreated macaques and 3 of 4 macaques given placebo gel, virus was recovered at every time-point tested. This indicates a very significant degree of protection ($P < .001$; Fisher's exact test). Virus was isolated on every occasion of testing from 2 of 3 animals where gel was administered 2 hours after virus challenge.[60]

Finally, limited vaginal PK tenofovir data in nonhuman primates demonstrate that tenofovir gel is broadly distributed in vaginal tissues following vaginal application and can penetrate to epithelial tissues.[96] The amount of tenofovir administered by intravaginal application of 4 grams (g) of a 1% dose (40 mg) is highly active against HIV and results in a reduction of plasma HIV ribonucleic acid (RNA) of 1.5 $\log_{10}$ copies/mL after daily administration for 21 days. There are no published studies of drug penetration into human colonic tissue after either rectal or oral administration of tenofovir, though these studies are ongoing. However, colon tissue penetration of tenofovir should exceed tenofovir vaginal tissue penetration given the single columnar colon epithelial layer in contrast to 40 cell layers in the stratified squamous epithelium of the vaginal mucosa.

Significant physiological, histological, and immunological heterogeneity exists within the gastrointestinal tract. The squamous epithelial mucosa of the esophagus is very different to the columnar epithelium of the small intestine. However, even within defined regions of the intestinal tract such as the large intestine there may be regional heterogeneity in histological and/or immunological function. As one example, the

predilection of ulcerative colitis (UC) to always extend from the distal rectum towards the cecum suggests that the left side of the colon has significant differences that make it more susceptible to UC than the right side of the colon. This heterogeneity, although poorly characterized, may have implications for the design of rectal microbicide safety studies. The anorectal tissue directly contacted during RAI (within 10 cm from anal verge) might be quite different to those areas not-directly traumatized but potentially in contact with seminal ejaculate (such as the proximal sigmoid colon).

HPTN 056 was a study of intestinal mucosal immune function.[11] The purpose of the study was to conduct a detailed evaluation of the short-term stability of a range of histological, immunological, and virological mucosal parameters in rectal biopsies obtained from HIV seronegative and seropositive men who were, or were not practicing, RAI. Tissue biopsies were collected at 10 cm and 30 cm from the anal verge. This study demonstrated that there was subtle regional heterogeneity in the expression of mucosal cell phenotypes. T cell populations recognized as target cells for HIV were more common in the 30 cm samples whereas cells bearing the B cell marker CD19 were more common in the 10 cm samples. Cytokine expression displayed less variability although IFN-γ was increased in the 10 cm samples from the individuals with HIV infection. However, these regional differences were felt to be modest and need to be replicated in other studies.

In MTN-007, we will compare biopsies collected at approximately 9 cm from the anal verge using anoscopy with samples collected at 15 cm using flexible sigmoidoscopy. This approach will allow us to evaluate potential regional heterogeneity between sites 9 and 15 cm from the anal margin. It will also allow us to determine whether anoscopy could be used as a primary sampling technique for future rectal microbicide safety studies. This would significantly advance the field by simplifying the sample collection procedures needed to conduct this type of study.

3 OBJECTIVES

3.1 Primary Objective

- To evaluate the safety of tenofovir 1% gel when applied rectally

3.2 Secondary Objectives

- To evaluate the acceptability of tenofovir 1% gel when applied rectally
- To evaluate the safety of placebo gel when applied rectally
- To determine whether use of tenofovir 1% gel is associated with rectal mucosal damage

- To determine whether use of 2% nonoxynol-9 gel (Gynol-II®) is associated with rectal mucosal damage

3.3 Exploratory Objectives

- To determine whether regional heterogeneity exists between mucosal endpoints in samples collected at 9 cm and 15 cm for all parameters examined

- To determine whether there is a correlation between histological abnormality and changes in mucosal biomarkers

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-007 is a Phase 1 randomized, double-blinded, multi-site, placebo-controlled trial. Approximately 60 participants will be randomized to the 4 study arms in a 1:1:1:1 ratio.

4.2 Summary of Major Endpoints

Primary

- Grade 2 or higher adverse events as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and/or Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies) to this table

Secondary

- The proportion of participants who at their Final Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during receptive anal intercourse

- Grade 2 or higher adverse events in the placebo gel arm, as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and/or Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies) to this table

- Changes in the following parameters:

    - Epithelial sloughing
    - Intestinal histopathology
    - Intestinal mucosal mononuclear cell phenotype
    - Intestinal mucosal cytokine messenger RNA (mRNA)

- Intestinal mucosal gene expression arrays
- Cytokine profile in rectal secretions
- Fecal calprotectin
- Microflora

Exploratory

- Changes in the following parameters

  - Epithelial sloughing
  - Intestinal histopathology
  - Intestinal mucosal mononuclear cell phenotype
  - Intestinal mucosal cytokine messenger RNA (mRNA)
  - Intestinal mucosal gene expression arrays
  - Cytokine profile in rectal secretions
  - Fecal calprotectin
  - Microflora

4.3 Description of Study Population

The study population will be healthy, HIV-uninfected men and women who meet criteria outlined in Section 5.2 and 5.3.

4.4 Time to Complete Accrual

Accrual is expected to be completed in approximately 5 months.

4.5 Study Groups

Four study arms are planned. A total of approximately 60 men and women will be randomized in a 1:1:1:1 ratio to tenofovir 1% gel, 2% N-9 gel, placebo gel, and no-treatment.

4.6 Expected Duration of Participation

Each participant will be on study for approximately 4 to 11 weeks. The total duration of the study will be approximately 8 months.

4.7 Sites

- Alabama Microbicide CRS, University of Alabama at Birmingham, Birmingham, AL, USA
- Fenway Community Health Center CRS, Boston, MA, USA
- Pitt CRS, University of Pittsburgh, Pittsburgh, PA, USA

5 STUDY POPULATION

5.1 Selection of Study Population

The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be utilized to ensure the appropriate selection of study participants for MTN-007.

5.1.1 Recruitment

Members of the research teams at some of the study sites will recruit men and women from various clinical sites at which they are providing direct patient care to potential study participants. Some sites will also recruit from the greater academic community and related catchment areas or will contact volunteers from previous research studies if those participants have previously signed an authorization permitting this type of contact. All three sites have experience in identifying and recruiting men who have sex with men (MSM) and women with a history of RAI into behavioral and/or clinical studies. Site Institutional Review Board (IRB)-approved media advertisements, telephone scripts, and fliers will be used. These materials will be presented and discussed with the community advisory boards (CAB) at all sites before submission to the local IRBs. Written informed consent will be obtained prior to the initiation of any study-related procedures.

5.1.2 Retention

Each site will establish participant retention procedures. Study site staff members at each site are responsible for developing and implementing site-specific standard operating procedures (SOP) for retention efforts.

5.2 Inclusion Criteria

Individuals who meet the following criteria are eligible for inclusion in the study:

1. ≥ Age of 18 at screening, verified per site SOP

2. Willing and able to provide written informed consent for screening and enrollment

3. HIV-1 uninfected at screening according to the standard DAIDS algorithm in Appendix II

4. Willing and able to communicate in English

5. Willing and able to provide adequate locator information, as defined in site SOP

6. Availability to return for all study visits, barring unforeseen circumstances

7. Per participant report at screening, a history of consensual RAI at least once in the prior year *(Required to assure that participants have a context for the acceptability assessments).*

8. Willing to abstain from insertion of anything rectally, including sex toys, other than the study gel for the duration of study participation

9. Willing to abstain from RAI for the duration of study participation

10. Must agree to use study provided condoms for the duration of the study for vaginal and insertive anal intercourse

11. Must be in general good health

12. At Screening and Enrollment, must agree not to participate in other research studies involving drugs, medical devices, or genital products for the duration of study participation (until all follow-up visits are completed)

In addition to the criteria listed above, female participants must meet the following criteria:

13. Postmenopausal or using (or willing to use) an acceptable form of contraception (e.g., barrier method, IUD, hormonal contraception, surgical sterilization, or vasectomization of male partner). If the female participant has female partners only, the method of contraception will be noted as a barrier method in the study documentation.

5.3 Exclusion Criteria

Individuals who meet any of the following criteria at screening will be excluded from the study:

1. Abnormalities of the colorectal mucosa, or significant colorectal symptom(s), which in the opinion of the clinician represents a contraindication to biopsy (including but not limited to presence of any unresolved injury, infectious or inflammatory condition of the local mucosa, and presence of symptomatic external hemorrhoids

2. At screening: participant-reported symptoms, and/or clinical or laboratory diagnosis of active rectal or reproductive tract infection requiring treatment per current CDC guidelines or symptomatic urinary tract infection (UTI). Infections requiring treatment include symptomatic bacterial vaginosis, symptomatic vaginal candidiasis, other vaginitis, trichomoniasis, Chlamydia (CT), gonorrhea (GC), syphilis, active HSV lesions, chancroid, pelvic inflammatory disease, genital sores or ulcers, cervicitis, or symptomatic genital warts requiring treatment. Note that an HSV-1 or HSV-2 seropositive diagnosis with no active lesions is allowed, since treatment is not required

Note: In cases of non-anorectal GC/CT identified at screening, one re-screening 2 months after screening visit will be allowed

3. Anorectal STI within six months prior to the Screening Visit

4. At screening:
    a. Positive for hepatitis B surface antigen
    b. Hemoglobin < 10.0 g/dL
    c. Platelet count less than 100,000/mm^3
    d. White blood cell count < 2,000 cells/mm^3 or > 15,000 cells/mm^3
    e. *For females:* calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula where creatinine clearance in mL/min (140- age in years) x (weight in kg) x (0.85 for female)/72 x (serum creatinine in mg/dL)
    f. *For males:* calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula where creatinine clearance in mL/min = (140 - age in years) x (weight in kg) x (1 for male)/72 x (serum creatinine in mg/dL)
    g. Serum creatinine > 1.3× the site laboratory upper limit of normal (ULN)
    h. Alanine transaminase (ALT) and/or aspartate aminotransferase (AST) > 2.5× the site laboratory ULN
    i. +1 glucose or +1 protein on urinalysis (UA)
    j. History of bleeding problems

5. History of significant gastrointestinal bleeding in the opinion of the investigator

6. Allergy to methylparaben, propylparaben, sorbic acid, and components of N-9

7. Known HIV-infected partners

8. By participant report at enrollment, history of excessive daily alcohol use (as defined by the CDC as heavy drinking consisting of an average consumption of more than 2 drinks per day for men, and more than 1 drink per day for women), frequent binge drinking or illicit drug use that includes any injection drugs, methamphetamines (crystal meth), heroin, or cocaine including crack cocaine, within the past 12 months

9. Per participant report at screening, anticipated use and/or unwillingness to abstain from the following medications during the period of study participation:
    a. Heparin, including Lovenox®
    b. Warfarin
    c. Plavix® (clopidogrel bisulfate)
    d. Rectally administered medications (including over-the-counter products)
    e. Aspirin
    f. Non-steroidal anti-inflammatory drugs (NSAIDS)
    g. Any other drugs that are associated with increased likelihood of bleeding following mucosal biopsy

10. By participant report at screening, use of post-exposure prophylaxis for HIV exposure, systemic immunomodulatory medications, rectally administered medications, rectally administered products (including condoms) containing N-9, or any investigational products within the 4 weeks prior to the Enrollment/Baseline Evaluation Visit and throughout study participation

11. History of recurrent urticaria

12. Any other condition or prior therapy that, in the opinion of the investigator, would preclude informed consent, make study participation unsafe, make the individual unsuitable for the study or unable to comply with the study requirements. Such conditions may include, but are not limited to, current or recent history of severe, progressive, or uncontrolled substance abuse, or renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, or cerebral disease

In addition to the criteria listed above, female participants will be excluded if they meet any of the following criteria:

13. Pregnant at the Enrollment/Baseline Visit

14. Breastfeeding at screening or intend to breastfeed during study participation per participant report.

6 STUDY PRODUCT

6.1 Regimen

Each participant will be randomized to one of three blinded study regimens or to no treatment. Participants randomized to a treatment arm will receive either tenofovir 1% gel, 2% nonoxynol-9 gel or placebo gel.

Treatment arm study participants will receive one dose of study product, at the Treatment 1 visit, under observation.

At the Treatment 2 visit, participants will receive a 7-day supply of study product to administer once daily. All participants will be instructed to insert the entire contents of one applicator rectally at night before bed, or before their longest period of rest.

There will be at least a 7-day washout period between the Treatment 1 and Treatment 2 visits. The participant will have a maximum of 28 days to initiate a consecutive 7-day regimen.

Table 7: Study Product Regimen

Arm	Description	N	Dose, Route, and Frequency
1	Tenofovir 1% gel	15	Entire contents of an applicator will be inserted rectally, for a total of 8 doses.
2	2% Nonoxynol-9 gel	15	Entire contents of an applicator will be inserted rectally, for a total of 8 doses.
3	Placebo gel	15	Entire contents of an applicator will be inserted rectally, for a total of 8 doses.
4	No treatment	15	Not Applicable

6.2 Administration

Study staff will instruct participants in proper methods of administering and storing their study product (tenofovir 1% gel, placebo gel or N-9 gel).

At the Treatment 1 Visit, participants will receive one applicator of their assigned study product for self-administration under observation of the site clinician/designee. At the Treatment 2 Visit the participants will receive 8 applicators of their assigned gel for the 7-day administration period. Participants are provided one extra applicator should an applicator not be useable for any reason. During the period of daily administration study participants will be instructed to insert one dose (the entire contents of one applicator) of gel into the rectum once daily throughout the 7-day period. Rectal administration of study product should occur before bedtime, usually in the evening, or the longest period of rest. Participants will be instructed to insert the gel as close to the same time each day as possible.

If a participant misses a dose, she/he must insert rectally the missed dose as soon as possible, unless the next dose is estimated to be due within 6 hours. If the next dose is estimated to be due within 6 hours, the missed dose must be skipped. The next dose will be inserted rectally as originally scheduled.

6.3 Study Product Formulation

6.3.1 Tenofovir 1% Gel

Tenofovir 1% gel (weight/weight) is a gel formulation of tenofovir (PMPA, 9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate), formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, and hydroxyethyl cellulose, with a pH adjusted to 4-5. Tenofovir 1% gel is a transparent, viscous gel that will be filled into applicators to form pre-filled, single-use applicators. Each pre-filled applicator will contain a dose of approximately 4.0 mL of tenofovir 1% gel (equal to 4.4 g).

Tenofovir 1% gel must be stored at controlled room temperature, 25°C (77°F), at all times. Excursions are permitted between 15°C and 30°C (59°F and 86°F).

6.3.2 2% Nonoxynol-9 Gel

Nonoxynol-9 (N-9) will be provided as Gynol II® (Johnson & Johnson, Fort Washington, PA). Gynol II® contains 2% nonoxynol-9 and inactive ingredients including lactic acid, methylparaben, povidone, propylene glycol, purified water, sodium carboxymethyl cellulose, sorbic acid and sorbitol sodium. Nonoxynol-9 is a non-ionic surfactant. It is the active ingredient in many commonly used over-the-counter contraceptive preparations (gels, creams, foams, films, sponges and suppositories) in the United States and worldwide. 2% N-9 will be filled into applicators to form pre-filled, single-use applicators. Each applicator will contain approximately 4.0 mL of 2% N-9 gel for delivery.

Two percent nonoxynol-9 should be stored at 20-25°C (68-77°F). Exposure to extremes of hot or cold should be avoided.

6.3.3 Placebo Gel

The placebo gel, sometimes called the "Universal Placebo Gel" contains hydroxyethyl cellulose as the gel thickener, purified water, sodium chloride, sorbic acid and sodium hydroxide.[48] The gel is isotonic and formulated at a pH of 4.4 to avoid disrupting the normal vaginal pH and has minimal buffering capacity to avoid the inactivation of sexually transmitted pathogens. Hydroxyethyl cellulose, the gelling agent, is used to approximate the viscosity of other microbicide gel candidates. Each pre-filled applicator will contain approximately 4 mL of Placebo gel for delivery.

Placebo Gel should be stored at 25°C (77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F).

6.4 Study Product Supply and Accountability

6.4.1 Study Product Supply

All study products will be available through Patheon Inc. Patheon Inc. will ship all study products directly to the pharmacist of record (PoR) at each study site. All study products must be stored in the pharmacy.

<u>Tenofovir 1% Gel</u>
Tenofovir 1% gel will be supplied by CONRAD (Arlington, VA, USA). Under direction from CONRAD, Patheon Inc., (Cincinnati, OH USA) which is a contract manufacturing facility, will manufacture the tenofovir 1% gel and analyze/release the gels under cGMP. Patheon Inc. will fill the applicators with tenofovir 1% gel to create pre-filled applicators and package each applicator and plunger in a wrapper.

Placebo Gel
The placebo gel will be supplied by CONRAD (Arlington, VA, USA). Under direction from CONRAD, Patheon Inc., (Cincinnati, OH USA) which is a contract manufacturing facility, will manufacture the placebo gel, and analyze/release the gels under cGMP. Patheon Inc. will fill the applicators with placebo gel to create pre-filled applicators and package each applicator and plunger in a wrapper.

2% Nonoxynol-9 Gel
The 2% nonoxynol-9 (N-9) will be supplied as Gynol II® manufactured by Johnson & Johnson (Fort Washington, PA, USA). DPT Laboratories LTD (San Antonio, TX, USA) will fill the applicators with 2% nonoxynol-9 to create pre-filled applicators and Patheon, Inc., will package each applicator and plunger in a wrapper.

6.4.2 Accountability

The PoR is required to maintain complete records of all study products received from Patheon Inc.

6.4.3 Dispensing

Study products are dispensed only to enrolled participants, upon receipt of a written prescription from an authorized prescriber. At Treatment 2 Visit, depending on the arm of the study to which the participant has been randomized, she/he will receive 8 pre-filled applicators containing tenofovir 1% gel, 2% N-9 gel or placebo gel.

The participants will be provided with sealable bags to collect and store all used and unused applicators, for return to the clinic.

6.4.4 Retrieval of Study Products

Unless the participant needs to replace an applicator, it is anticipated that one unused applicator should remain after the 7 consecutive days of administration. Study participants will be instructed to return all used and unused applicators to the site at the Final Visit. Study staff will count and document the number of returned used and unused applicators. The **used** applicators will be stored at the study site in a biohazard container. The **unused** applicators will be sent to the pharmacy and will be placed in quarantine until returned.

6.4.5 Male Condoms and Lubricant

All participants will receive male condoms and participants in the treatment arm will be offered study specified lubricant to aid with applicator insertion. The condoms and lubricant will be dispensed by the clinic staff, and made available in the clinic.

6.5 Assessment of Participant Adherence

Adherence to product use is crucial to a study that seeks to determine product safety. To encourage adherence, participants will be instructed to apply the product daily before bedtime, usually in the evening or before longest period of rest given that this is likely to result in less leakage and soiling of underwear than is likely to occur when participants are walking around in the course of their daily activities. Therefore, we expect that product administration prior to the longest period of rest will result in better adherence. To monitor adherence, participants will be asked to use a phone reporting system (PRS) after each episode of gel use. To access the PRS, participants call a toll-free number, identify themselves to the system using a unique ID number (corresponding to the participant identification number (PTID)), and then respond to pre-recorded questions on product use and whether there is any comment related to this particular occasion of product use. Responses can be entered by either pressing keys (1 for yes, 2 for no) or by voice response that is understood and registered by the system. Participants receive a small monetary incentive for each call regardless of their report of product use or lack of use; furthermore, a bonus at the end of the seven days is accrued by those who have not missed any day in calling the system. When participants do not call the system within 48 hours, an alert is automatically generated and sent by email to a staff member at Columbia University. The staff member at Columbia University will then contact the study coordinator at the study site who then contacts the participant to inquire about missed calls (if the participant forgot to call) and adherence to the study product regimen. Thus, this system allows monitoring of adherence to calling the PRS on a time-stamped basis. Given that participants are instructed to use the product at bedtime and to call the system immediately after applying the product, the calls are a proxy for compliance with time of application; plus, participants will be reporting whether they used the product, which will constitute one measure of study product adherence. Since participants will be asked to return in separate, sealed bags both used and unused applicators, we will be able to cross validate self-reports, and applicator counts to assess adherence.

6.6 Concomitant Medications

With the exception of medications listed as prohibited, enrolled study participants may use concomitant medications during study participation. All concomitant medications, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs, and herbal preparations reported throughout the course of the study will be recorded on case report forms designated for that purpose.

6.7 Prohibited Medications and Practices

Study participants will be prohibited from using the following medications throughout the study period: heparin (including Lovenox®), warfarin, Plavix® (clopidogrel bisulfate), rectally administered medications (including over-the-counter products), aspirin or NSAIDS, and other drugs that are associated with increased likelihood of bleeding following mucosal biopsy. Furthermore, study participants will be advised not to use the

following products within 4 weeks of the Enrollment/Baseline Evaluation Visit and throughout study participation: post-exposure prophylaxis for HIV exposure, systemic immunomodulatory medications, rectally administered medications, rectally administered products containing N-9, or any other investigational products. Should participants report use of any of these medications or products, PSRT consultation will be requested regarding use of study product. In the event that a participant reports NSAID use prior to a visit requiring endoscopy or biopsy, the study visit should be rescheduled where possible. If not, the determination of action must be decided via an emergency PSRT consultation.

Participants will be advised to refrain from any practices which include rectal insertion of any product including those used during sexual intercourse (sex toys).

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is presented in Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites are provided in the study-specific procedures manual. Unless otherwise specified, the laboratory procedures listed in this section are performed at the local study site laboratories.

In addition to any Interim Visits that may occur in accordance with guidance outlined in Section 7.9, the following visits should take place for study participants:

- Screening (Visit 1)
- Enrollment/Baseline Evaluation (Visit 2)
- Treatment 1 (Visit 3)
- Follow-Up Phone Assessment (Visit 4)
- Treatment 2 (Visit 5)
- Final (Visit 6)
- Follow-up Phone Assessment/Termination Visit (Visit 7)

Participants randomized to treatment arms will receive a single dose of study product at the Treatment 1 Visit, and then will receive a 7-day supply of study product at the Treatment 2 Visit. Participants will be instructed to insert the study product at night before bed, or before their longest period of rest. There is a 7-day washout period between the Treatment 1 and Treatment 2 Visits. The Enrollment/Baseline Evaluation Visit will be considered Day 0 and will occur no more than 36 days following the Screening Visit.

7.1 Screening Visit

Written informed consent will be obtained before any screening procedures are initiated. For participants who do not meet the eligibility criteria, screening will be discontinued

once ineligibility is determined. For participants who are found to be presumptively eligible based on the evaluations at Screening (listed below), final eligibility will be confirmed at the Enrollment/Baseline Evaluation Visit, which must take place no more than 36 days following the Screening Visit.

Table 8: Screening Visit

Screening Visit	
Component	**Procedure/Analysis**
Administrative	• Obtain written informed consent for Screening Visit • Assign participant ID (PTID) • Collect demographic information • Collect locator information • Assess eligibility • Provide reimbursement for study visit • Schedule next study visit*
Clinical	• Collect medical history (including exclusionary medical conditions and medications) • Document pre-existing conditions • Collect menstrual history♀ • Collect concomitant medications • Perform physical exam • Perform rectal exam • Provide counseling o HIV pre-and post-test o HIV/STI risk reduction o Contraceptive • Provide condoms • Treat for UTI/RTIs/STIs or refer for other findings*
Urine	• Collect urine sample o ♀ Qualitative hCG o Dipstick urinalysis (UA) for protein, glucose, nitrites, and leukocyte esterase o GC and CT by nucleic acid amplification testing (NAAT)
Blood	• Collect blood specimens o CBC with differential and platelets o BUN, creatinine (calculate creatinine clearance), ALT, AST o Syphilis rapid plasma reagin (RPR) (confirmatory tests as needed) o HIV-1 serology (confirmatory tests as needed) o Hepatitis B surface antigen (HBsAg) o HSV serology
Rectal Specimens	• Rectal swabs o Rectal GC/CT by NAAT

*if indicated ♀ for females of childbearing potential

7.2 Enrollment/Baseline Evaluation Visit

The Enrollment Visit (Day 0) will occur within 36 days of the Screening Visit.

Table 9: Enrollment/Baseline Evaluation Visit (Day 0, Within 36 Days of Screening Visit)

Enrollment/Baseline Evaluation Visit	
Component	**Procedure/Analysis**
Administrative	• Obtain written informed consent for Enrollment and Storage and Future Testing of Specimens • Review/update locator information • Provide test results • Eligibility confirmation • Randomization • Provide reimbursement for study visit • Schedule next study visit
Clinical	• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform physical exam • Perform rectal exam • Document pre-existing conditions • Provide counseling o Adherence (protocol) o HIV pre-and post-test* o HIV/STI risk reduction o Contraceptive • Provide condoms • Treat for UTI/RTIs/STIs or refer for other findings*
Behavioral Assessment	• Administer Baseline Behavioral Questionnaire (BBQ) to all participants o Instruct participant in use of web-based questionnaire
Urine	• Collect urine sample o Qualitative hCG♀ o GC/CT by NAAT*
Blood	• Collect blood specimens o Syphilis RPR (confirmatory tests as needed)* o HIV-1 serology (confirmatory tests as needed)* o Plasma archive
Rectal Specimens	• Rectal swabs o Rectal swab for microflora o Rectal GC/CT by NAAT* • Collect rectal sponge specimen for cytokines • Administer preparatory Normosol-R pH7.4 enema o Collect effluent for assessment of epithelial sloughing and fecal sample for calprotectin • Perform high resolution anoscopy and collect: o Approximately 7 rectal biopsies at approximately 9 cm for histology, cytokine RT PCR, mucosal T cell phenotyping, and mucosal gene expression arrays • Perform flexible sigmoidoscopy and collect: o Approximately 7 rectal biopsies at approximately 15 cm for histology, cytokine RT PCR, mucosal T cell phenotyping, and mucosal gene expression arrays

*If indicated; ♀ for females of childbearing potential

7.3 Treatment 1 Visit

The Treatment 1 Visit will occur between Day 7 and Day 28.

Table 10: Treatment 1 Visit

Treatment 1 Visit	
Component	**Procedure/Analysis**
Administrative	• Review/update locator information • Test results* • Provide reimbursement for study visit • Schedule next study visit • Schedule follow-up phone assessment

Clinical	• Review/update medical history
	• Review/update menstrual history♀
	• Review/update concomitant medications
	• Perform physical exam
	• Perform rectal exam
	• Provide counseling
	  o Adherence (protocol) including RAI abstinence
	  o HIV/STI risk reduction
	  o Contraceptive
	• Provide condoms
	• Record adverse events
	• Treat for UTI/RTIs/STIs or refer for other findings*

Urine	• Collect urine sample
	  o Qualitative hCG♀
	  o GC/CT by NAAT*

Rectal Specimens	• Rectal swabs
	  o Rectal swabs for microflora
	  o Rectal GC/CT by NAAT*
	• Collect rectal sponge specimen for cytokines
	• Administer preparatory Normosol-R pH 7.4 enema
	  o Collect effluent for assessment of epithelial sloughing and fecal sample for calprotectin
	• Perform high resolution anoscopy and collect:
	  o Approximately 7 rectal biopsies at approximately 9 cm for histology, cytokine RT PCR, mucosal T cell phenotyping, and mucosal gene expression arrays
	• Perform flexible sigmoidoscopy and collect:
	  o Approximately 7 rectal biopsies at approximately 15 cm for histology, cytokine RT PCR, mucosal T cell phenotyping, and mucosal gene expression arrays

Study Product Supply	• Observe participant administration of single dose of tenofovir 1% gel, 2% N-9 gel, or placebo gel and offer study lubricant to participants in treatment arm

*If indicated; ♀ for females of childbearing potential

7.4 Follow-Up Phone Assessment

A follow-up phone assessment will be scheduled to take place within approximately 24 hours of the Treatment 1 Visit. Study staff will follow-up with participants to inquire about AEs they might experience as a result of study product or procedures performed during the Treatment 1 Visit.

Table 11: Follow-Up Phone Assessment

Follow-up Phone Call	
Component	**Procedures/Analysis**
Clinical	• Record AEs

7.5 Treatment 2 Visit

The Treatment 2 Visit will occur between Days 14 and 42, but at least 7 days after the Treatment 1 Visit.

Table 12: Treatment 2 Visit

Treatment 2 Visit	
Component	**Procedure/Analysis**
Administrative	• Review/update locator information • Test results* • Provide reimbursement for study visit • Schedule next study visit
Clinical	• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform physical exam* • Perform rectal exam* • Provide counseling o HIV/STI risk reduction o Contraceptive o Adherence (protocol and product use) • Provide condoms • Record/update AEs • Treat for UTI/RTIs/STIs or refer for other findings*
Behavioral Assessment	• Provide instructions on use of Phone Reporting System to participants randomized to treatment arm
Urine	• Collect urine sample o Qualitative hCG♀ o GC/CT by NAAT*
Rectal Specimens	• Rectal swabs o Rectal GC/CT by NAAT* • Perform high resolution anoscopy and collect*: o Approximately 7 rectal biopsies at approximately 9 cm for histology, cytokine RT PCR, and mucosal T cell phenotyping, and mucosal gene expression arrays
Study Product Supply	• Provide supply of tenofovir 1% gel, 2% N-9 gel, or placebo gel and offer study lubricant to participants in treatment arm

*If indicated; ♀ hCG for females of childbearing potential

7.6 Final Clinic Visit

The Final Clinic Visit will occur between Day 21 and Day 63, on the day after the last dose of study product, and no more than 21 days after the Treatment 2 Visit.

Table 13: Final Clinic Visit

Final Visit	
Component	**Procedure/Analysis**
Administrative	• Review/update locator information • Schedule follow-up phone assessment • Provide reimbursement for study visit • Provide test results*
Clinical	• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform physical exam • Perform rectal exam • Provide counseling o HIV pre-and post-test counseling o HIV/STI risk reduction • Provide condoms • Record/update AEs • Treat for UTI/RTIs/STIs or refer for other findings*
Behavioral Assessment	• Administer Product Acceptability Questionnaire (web-based) to participants randomized to treatment arm
Urine	• Collect urine sample o Qualitative hCG♀ o Dipstick U/A o GC/CT by NAAT*
Blood	• CBC with differential and platelets • BUN, creatinine, ALT, AST • Syphilis RPR (with confirmatory tests as needed) • HIV serology (with confirmatory tests as needed)
Rectal Specimens	• Rectal swabs o Rectal GC/CT by NAAT* o Rectal microflora • Collect rectal sponge specimen for cytokines • Administer preparatory Normosol-R pH 7.4 enema o Collect effluent for assessment of epithelial sloughing and fecal sample for calprotectin • Perform high resolution anoscopy and collect: o Approximately 7 rectal biopsies at approximately 9 cm for histology, cytokine RT PCR, and mucosal T cell phenotyping, and mucosal gene expression arrays • Perform flexible sigmoidoscopy and collect: o Approximately 7 rectal biopsies at approximately 15 cm for histology, cytokine RT PCR, and mucosal T cell phenotyping, and mucosal gene expression arrays
Study Product Supply	• Collect used and unused product from participants in treatment arm

*If indicated ♀ for females of childbearing potential

7.7 Follow-up Phone Assessment Visit/Termination Visit

The Follow-up Phone Assessment Visit will occur between days 28 and 77, targeted to occur 7 days after the Final Clinic Visit and no more than 14 days after the Final Clinic Visit.

Table 14: Follow-Up Phone Assessment Visit

Phone Assessment (Visit 6)	
Component	**Procedure/Analysis**
Clinical	• Record/update AEs

7.8 Follow-up Procedures for Participants Who Discontinue Study Product

Participants who permanently discontinue study product will not routinely be withdrawn from the study. Rather, every effort will be made to complete all protocol-specified visits and procedures with these participants with the exceptions described below.

7.8.1 Participants Who Become Infected with HIV

Study staff will capture seroconversions on study case report forms (CRFs). Protocol-specified procedures will continue except:

- HIV serology
- Provision of study product
- Adherence counseling (protocol and product use)
- Counseling for HIV/STI risk reduction. Counseling will be modified to address primary and secondary HIV/STI prevention for infected individuals.
- Anoscopy (only if clinically indicated)
- Flexible sigmoidoscopy (only if clinically indicated)

7.8.2 Participants Who Become Pregnant

All protocol-specified study procedures will continue except:

- Provision of study product
- Adherence counseling (protocol and product use)
- Rectal exam
- Anoscopy (only if clinically indicated)
- Flexible sigmoidoscopy (only if clinically indicated)
- Rectal swabs
- Qualitative hCG
- Contraceptive counseling

7.8.3 Participants Who Voluntarily Discontinue Study Product

All protocol-specified study procedures will continue except:

- Provision of study product
- Adherence counseling (protocol and product use)
- Anoscopy (only if clinically indicated)

- Flexible sigmoidoscopy (only if clinically indicated)

7.8.4 Participants Who Are Discontinued from Study Product by the Site Investigator

All protocol-specified study procedures will continue except:

- Provision of study product
- Adherence counseling (protocol and product use)
- Anoscopy (only if clinically indicated)
- Flexible sigmoidoscopy (only if clinically indicated)

Table 15: Early Termination Visit

Early Termination Visit	
Component	**Procedure/Analysis**
Administrative	• Review/update locator information • Schedule follow-up phone assessment* • Provide reimbursement for study visit • Provide test results*
Clinical	• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform physical exam • Perform rectal exam • Provide counseling o HIV pre-and post-test counseling o HIV/STI risk reduction • Provide condoms • Record/update AEs • Treat for UTI/RTIs/STIs or refer for other findings*
Behavioral Assessment	• Administer Product Acceptability Questionnaire (web-based) to participants in treatment arm
Urine	• Collect urine sample o Qualitative hCG♀ o Dipstick U/A o GC/CT by NAAT*
Blood	• CBC with differential and platelets • BUN, creatinine, ALT, AST • Syphilis RPR (with confirmatory tests as needed) • HIV serology (with confirmatory tests as needed)
Rectal Specimens	• Rectal swabs o Rectal GC/CT by NAAT* • Perform high resolution anoscopy and collect:* o Approximately 7 rectal biopsies at approximately 9 cm for histology, cytokine RT PCR, and mucosal T cell phenotyping, and mucosal gene expression arrays • Perform flexible sigmoidoscopy and collect*: o Approximately 7 rectal biopsies at approximately 15 cm for histology, cytokine RT PCR, and mucosal T cell phenotyping, and mucosal gene expression arrays
Study Product Supply	• Collect used and unused product from participants in treatment arm

*if indicated; ♀ for females of childbearing potential

7.9 Interim Contacts and Visits

Interim visits may be performed at any time during the study. All interim contacts and visits will be documented in participants' study records and on applicable case report forms.

Some Interim Visits may occur for administrative reasons. For example the participant may have questions for study staff. 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.

Table 16: Interim Contacts and Visits

Interim Contacts and Visits	
Component	**Procedure/Analysis**
Administrative	• Review/update locator information • Provide test results* • Schedule next visit*
Clinical	• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform physical exam* • Perform rectal exam* • Provide counseling o HIV pre-and post-test counseling* o HIV/STI risk reduction • Provide condoms • Record/update AEs* • Treat for UTI/RTIs/STIs or refer for other findings*
Urine	• Collect urine sample o Qualitative hCG♀ o Dipstick U/A* o GC/CT by NAAT*
Blood	• CBC with differential and platelets* • BUN, creatinine, ALT, AST* • Syphilis RPR (with confirmatory tests as needed)* • HIV serology (with confirmatory tests as needed)*
Rectal Specimens	• Rectal swabs o Rectal GC/CT by NAAT* • Perform high resolution anoscopy and collect:* o Approximately 7 rectal biopsies at approximately 9 cm for histology, cytokine RT PCR, and mucosal T cell phenotyping, and mucosal gene expression arrays • Perform flexible sigmoidoscopy and collect*: o Approximately 7 rectal biopsies at approximately 15 cm for histology, cytokine RT PCR, and mucosal T cell phenotyping, and mucosal gene expression arrays
Study Product	• Collect unused study product from participants in treatment arm*

*if indicated; ♀ for females of childbearing potential

7.10 Final Contact

The Final Clinic Visit for all participants will include laboratory testing for complete blood count, liver panel, creatinine level, and HIV. If all results are not available at the Follow-up Phone Assessment/Termination Visit, a final contact (in person or by telephone – except for HIV test results) may be required to provide these study test results, and post-test counseling, if needed. In addition, for participants who become pregnant during study participation, an additional contact may be required to ascertain the participant's pregnancy outcome. All final contacts will be documented in participant study records.

7.11 Clinical Evaluations and Procedures

The following physical and rectal exam components will be conducted at select visits.

Physical Exam

- Height (may be omitted after the Screening Visit)
- Weight
- Vital signs
    - Temperature
    - Pulse
    - Blood pressure
- General appearance
- Abdomen
- Other components as indicated by participant symptoms

Medical History

- Each participant will be asked about any symptoms or AEs experienced since their previous visit

Rectal Exam and Rectal Specimen Collection

The participant will be positioned in the left lateral decubitus position for the following procedures:

Rectal Exam

- Visual and digital rectal exam: The examiner will conduct a visual examination of the anus and surrounding area and note any abnormality. The examiner will then insert a lubricated gloved finger into the anal canal and sweep around the internal anal circumference.

Rectal Specimen Collection

- Rectal swabs GC/CT, microflora, and sponge collection for cytokines: A lubricated plastic anoscope will be gently and fully inserted (until the lateral 'wings' touch the anal margin) and the obturator removed. Swabs for GC/CT and microflora will be sequentially inserted through the anoscope and placed in contact with the rectal wall, turned through 360 degrees and removed. Next, the

sponge will be inserted through the anoscope and placed in contact with rectum and remain there for 5 minutes. The sponge will then be removed and packaged, then the anoscope will be slowly removed

- Rectal lavage: A 120 mL Normosol-R® (Hospira Inc., Lake Forest, IL) enema will be inserted through the anus and the contents squeezed into the rectum. The participant will hold the fluid in the rectum for approximately 5 minutes then expel it, including stool, into a collection device placed over a toilet bowl
- Flexible sigmoidoscopy and biopsy: A flexible sigmoidoscope will be inserted to 15 cm and biopsies taken using biopsy forceps
- Anoscopic biopsy: A lubricated anoscope will be inserted into the anorectum until the 'wings' touch the anal verge. Biopsies will be taken at 9 cm using biopsy forceps

7.12 Behavioral Measures

There will be three sets of behavioral measures used in this protocol:

Baseline Behavioral Questionnaire

This is a Web-based self-interview that all participants will complete at the Enrollment/Baseline Evaluation Visit at a computer terminal located in the research offices. In addition to demographics, this questionnaire assesses participants' sexual behavior in the prior three months with HIV-negative, positive, or unknown status men and women, including among men, their sexual role—insertive, receptive, or versatile, and frequency of condom use.[97] The assessment includes questions on use of hyperosmolar or hypo-osmolar rectal lubricants, rectal douching prior to sexual intercourse, use of lubricants containing N-9, and other behavioral practices that may affect the anal sphincter or rectal compartment. It also includes questions on frequency of alcohol and drug use in the prior three months and frequency of HIV testing. Finally, the assessment explores participants' attitudes about pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), knowledge about microbicides and likelihood of using a microbicide in the future.

Adherence Questionnaire

Adherence will be assessed with PRS to which participants who are randomized to the treatment arm, will be asked to call daily (as described in Section 6.5). Responses to specific questions on product use since the prior call (e.g., "Did you use the product? Y/N) will constitute a measure of adherence. This measurement will be cross validated with used/unused returned applicator counts. In addition, at the Final Clinic Visit, participants will be asked to report on study product use via the Web-based self-interview.

Product Acceptability Questionnaire

This Web-based self-interview will be completed by participants randomized to the treatment arm at the Final Clinic Visit. This questionnaire includes structured and semi-structured questions about the experiences the participant had using the gel rectally, likes and dislikes concerning the gel, the applicator, and the application process, any

changes she/he may have introduced or may wish to introduce in the product used, any problems (e.g., leakage, soiling) she/he may have had, or other product side-effects and how much the participant was bothered by them, and likelihood of using a rectally applied microbicide in the future. This last section has items worded similarly to those of the same section administered at baseline so that we will be able to compare the anticipated likelihood of product use before and after participants become familiar with a product.

7.13 Laboratory Evaluations

7.13.1 Local Laboratory Testing

The local laboratory, site investigator, or designee will run the following, as indicated:

- CBC with platelets and differential
- Syphilis testing by RPR with confirmatory testing as needed
- BUN, creatinine, AST, ALT
- HIV-1 serology, with confirmatory testing as needed
- Urine hCG for women
- Urinalysis
- Urine GC/CT by NAAT
- Hepatitis B surface antigen
- HSV serology
- Rectal GC/CT by NAAT

7.13.2 Network Laboratory Testing

The NL will run the following as indicated:

- Rectal swabs
    - Microflora
- Rectal sponge for cytokines (Luminex)
- Rectal lavage for sloughing
- Rectal biopsies by high resolution anoscopy (HRA) and flexible sigmoidoscopy
    - Cytokines (RT PCR)
    - Gene expression microarrays
    - Phenotyping (flow cytometry)
    - Histology
- Blood Specimens:
    - Plasma archive (to confirm HIV serostatus)

7.13.3 Genova Diagnostics

Fecal specimens will be collected and shipped to Genova Diagnostics for analysis

- Fecal sample (calprotectin)

7.14 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical laboratory practice, the HPTN-MTN Network Laboratory Manual (www.mtnstopshiv.org),DAIDS Laboratory Requirements (http://www3.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Laboratories.htm), MTN-007 Study Specific Procedures Manual (www.mtnstopshiv.org), and site 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 when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

7.15 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/LabPolicy.pdf)

7.16 Storage of Specimens for Future Use

The mucosal biopsy samples will be processed for histology, cell isolation and flow cytometry, and RNA isolation. Histology blocks will be stored at the MTN Core laboratory in Pittsburgh. The cells isolated from the gut biopsies will be consumed by the flow cytometry process and there will be no residual cells. The RNA will be used for RT-PCR amplification in Pittsburgh and for gene array studies at the MTN immunology core in Seattle. It is anticipated that there will be residual RNA stored in both Seattle and Pittsburgh. The residual RNA samples are needed to facilitate additional RT-PCR evaluation of genes identified in the gene array studies. After all protocol testing is complete, any residual samples will be stored based on initial consent from the participant. If the participant did not give consent to store samples after completion of the study, each site will discard specimens according to institute policy.

7.17 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by US Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

The study site investigators are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Chair, CONRAD Medical Officer (MO), DAIDS MO, Protocol Safety Physicians, and Clinical Affairs Safety Associate, serves as the Protocol Safety Review Team (PSRT). The MTN Statistical Data and Management Center (SDMC) prepares routine safety data reports (blinded to treatment assignment) for review by the PSRT, which meets via conference call approximately twice per month during the first 6 months of the study, and then as needed throughout the period of study implementation to review safety data, discuss product use management, and address any potential safety concerns.

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.

During the trial, the PSRT will review safety reports (blinded to treatment assignment) and conduct calls to review the data as appropriate. The content, format and frequency of the safety 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-007 PSRT.

A Study Monitoring Committee (SMC) has study oversight as no Data Safety Monitoring Board (DSMB) is planned for this study. The SMC provides review of key performance indicators such as participant accrual, participant retention, protocol and intervention adherence, data quality and laboratory quality. As this is a Phase 1 study, the SMC is also charged with reviewing participant safety data.

The SMC will review the study within the first four to six months of the study implementation and at least every six months thereafter (unless review is waived by the SMC Chair).

If at any time, a decision is made to discontinue study gel in all participants, CONRAD, after consultation with the protocol team will inform the US Food and Drug Administration (FDA). The Site PIs will notify the responsible IRBs expeditiously.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An adverse event 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 is applied to all the study groups, and is applied to all groups beginning from the time of randomization. The term “investigational product” for this study refers to all three study products listed in Section 6 plus the gel applicator.

Study participants will be instructed to contact the study site staff to report any AEs they may experience at any time between enrollment and completion of their participation. In the case of a life-threatening event, they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where the study clinician is based, and to request that the clinician be contacted upon their arrival. Sites will obtain written permission from the participant to obtain and use records from non-study medical providers to complete any missing data element on a CRF related to an adverse event. All participants reporting an untoward medical occurrence will be followed clinically, until the occurrence resolves (returns to baseline) or stabilizes.

The site IoR will determine AE resolution or stabilization in their best clinical judgment, but may seek DAIDS MO and/or PSRT medical consultation regarding follow-up or additional evaluations of an AE. Study site staff will document in source documents all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. Study staff also will record all AEs on case report forms. The DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009), Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies) will be the primary tools for grading adverse events for this protocol. Adverse events not included in that table will be graded by the DAIDS AE Grading Table, Version 1.0 December 2004 (Clarification dated August 2009). In cases where an AE is covered in multiple tables, Addendum 3 (Rectal Grading Table for Use in Microbicide Studies) will be the grading scale utilized. Please note that the grading scale for proteinuria should also be used for grading glycosuria.

Even though RAI abstinence is a requirement during the trial, participants will be encouraged to report to the study clinician any problems experienced by their partners that might be potentially related to study product. If any such problems are reported, study staff should evaluate and document the occurrence. Should any concerns arise with regard to partner safety; the Protocol Chair will advise all study sites on appropriate action.

8.3.2 Serious Adverse Events

Serious adverse events (SAEs) will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, dated January 2010) as AEs occurring at any dose that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
  Note: Per ICH SAE definition, hospitalization itself is not an adverse event, but is an outcome of the event. Thus, hospitalization in the absence of an adverse event is not regarded as an AE, and is not subject to expedited reporting. The following are examples of hospitalization that are not considered to be AEs:
  - Protocol-specified admission (e.g. for procedure required by study protocol)
  - Admission for treatment of target disease of the study, or for pre-existing condition (unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator)
  - Diagnostic admission (e.g. for a work-up of an existing condition such as persistent pretreatment lab abnormality)
  - Administrative admission (e.g. for annual physical)
  - Social admission (e.g. placement for lack of place to sleep)
  - Elective admission (e.g. for elective surgery)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.3.3 Adverse Event Relationship to Study Product

The relationship of all AEs to study product will be assessed per the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, dated January 2010), the tenofovir gel investigator's brochure, the N-9 package insert, the placebo gel investigator's brochure, and clinical judgment. Per the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, dated January 2010), the relationship categories that will be used for this study are:

- *Related*: There is a reasonable possibility that the AE may be related to the study agent(s)

- *Not related*: There is not a reasonable possibility that the AE is related to the study agent(s)

8.4 Expedited Adverse Event (EAE) Reporting Requirements

Expedited Adverse Event Reporting

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/. The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

EAE reporting procedures specific to this protocol are that once the sites have submitted EAEs via DAERS (as above), the RSC Safety Office will also prepare the draft safety reports and send them to the CONRAD and DAIDS MOs for review.

Study sites will be contacted by the DAIDS MO if any further information or clarification is needed after the report is evaluated by CONRAD and DAIDS MOs. The RSC Safety Office will then prepare the final report which will go to CONRAD for signature and submission to the FDA. Copies of this final report will be filed with CONRAD and RSC. Additionally, the RSC Safety Office will distribute safety reports to all DAIDS sites that use products under investigation in this study.

For all EAEs submitted, sites must file an RSC update with the final or stable outcome unless the initial EAE submitted had a final or stable outcome noted already.

EAE Reporting Requirements for this Study

The SAE EAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agents for which expedited reporting to CONRAD and the DAIDS MO are required are: tenofovir 1% gel, 2% nonoxynol-9 gel, placebo gel, and the gel applicator.

Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies) will be the

primary tools for grading adverse events for this protocol. Adverse events not included in those tables will be graded by the DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009). In cases where an AE is covered in all tables, the DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification dated August 2009), Addendum 3 (Rectal Grading Table for Use in Microbicide Studies) will be the grading scale utilized.

The DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification dated August 2009), and Addenda 1 and 3 are available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

EAE Reporting Period

- The expedited AE reporting period for this study is defined as the entire study duration for an individual participant (from study enrollment until the participant's final study contact (Follow-Up Phone Assessment Visit/Termination Visit).
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.5 Pregnancy and Pregnancy Outcomes

Pregnant participants are excluded from this study. Routine urine testing is performed at every study visit. If participants become pregnant at any time during the course of the study, study agents are discontinued, but participants will remain in the study and will continue with these assessments: UA, acceptability assessments, HIV serology, and safety bloods.

Pregnancy-related data will be collected using the pregnancy CRFs for all pregnancies detected during the study. Pregnancy outcomes will not be expeditiously reported to CONRAD and the DAIDS MO unless there is an associated adverse event in the pregnant participant that meets expedited reporting criteria or the pregnancy results in a congenital anomaly meeting the Manual for Expedited Reported of Adverse Events to DAIDS (Version 2.0, January 2010) guidelines for expedited reporting. Fetal losses without congenital anomalies or maternal complications that require expedited reporting will not be expeditiously reported but data will be captured via the pregnancy CRFs.

After the participant's final study contact (Follow-Up Phone Assessment Visit/Termination Visit), pregnancy outcomes that meet criteria for EAE reporting as described above (e.g., maternal complications, congenital anomalies) occurring among participants known to be pregnant at the Final Study Visit will continue be expeditiously reported. The SDMC will prepare and provide to CONRAD a quarterly report on all pregnancies and their outcomes. The SDMC will also prepare an annual summary report of all AEs for the annual IND reports (submitted by CONRAD).

8.6 Social Harms Reporting

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. Social harms that are judged by the Investigator of Record to be serious or unexpected will be reported to responsible site IRB at least annually, or according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. While maintaining participant confidentiality, study sites may engage their CABs in exploring the social context surrounding instances of social harm.

9 CLINICAL MANAGEMENT

Guidelines for clinical management and product discontinuation are outlined in this section.

In general, the site investigator has the discretion to discontinue study product at any time if she/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. Unless otherwise specified below, the investigator should immediately consult the PSRT for further guidance regarding permanent discontinuation.

The site investigator or designee will document all discontinuations on applicable case report forms.

9.1 Grading System

The primary grading system is located in the Rectal Grading Table for Use in Microbicide Studies, which is labeled as Addendum 3 in the DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification dated August 2009), which can be found on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

9.3 Discontinuation of Study Product(s) in the Presence of Toxicity

Grade 1 or 2
In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study product that is not specifically addressed below may continue use of study products per protocol.

Grade 3
Participants who develop a Grade 3 AE or toxicity that is not specifically addressed below and is judged to be related to study product should have that study product permanently discontinued.

Grade 4
Participants who develop a Grade 4 AE or toxicity that is not specifically addressed below (regardless of relationship to study product) should have the current study product permanently discontinued.

9.4 General Criteria for Discontinuation of Study Product

Study participants will be permanently discontinued from product use by the Site Investigator or designee in the event of the following:

- Pregnancy
- HIV seroconversion

9.5 Management of Specific Adverse Events

9.5.1 Hemorrhage Following Rectal Mucosal Biopsy

If bleeding continues after the flexible sigmoidoscopy/HRA procedure that is uncontrolled (occurring between bowel movements) and results in the passage of blood clots per rectum, the participant will be referred for assessment in the emergency department of the nearest hospital.

9.5.2 Infection Following Rectal Mucosal Biopsy

The rate of local or systemic infection following anorectal biopsy is very low (< 1 per 1,500 - R Cranston personal communication). Any participant presenting with local or systemic features compatible with infection (fever, localized anorectal pain, anal discharge) will be referred to the emergency department of the nearest hospital.

9.5.3 Perforation of Rectum Following Rectal Mucosal Biopsy

The rate of perforation of a hollow viscus following endoscopic biopsy is less than 0.88:1,000[98]. However, anoscopic rectal sampling is even less likely to perforate a hollow viscus due to sampling being below the reflection of the pelvic peritoneum and

the absence in insufflation for the procedure. Any participant presenting with local or systemic clinical features suggestive of this condition (abdominal pain, swelling, fever) will be referred to the emergency department of the nearest hospital.

9.6 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The site investigator also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRP. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the Office of Human Research Protections), or site IRBs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume product use (if applicable) and follow-up through their originally scheduled study exit date.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is a Phase 1 randomized, double-blinded, multi-site, placebo-controlled safety and acceptability study of tenofovir 1% gel. Sixty RAI abstinent, HIV negative adults (male and female) from three sites will be recruited and randomized to four study arms (15 per arm). Participants randomized to a treatment arm will first receive a single dose of the study gel administered rectally in the clinic. Within 30 minutes, a specimen will be obtained to evaluate the mucosal damage by the gel. After a one week recovery period, participants will self-administer rectally outpatient doses once daily for 7 days. They will return to the clinic for acceptability evaluation and specimen collection.

10.2 Study Endpoints

10.2.1 Primary Endpoint

Consistent with the primary study objectives to evaluate the safety of tenofovir 1% gel when applied rectally, the following endpoints will be assessed:

- Grade 2 or higher adverse events as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and/or Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies)

10.2.2 Secondary Endpoints

Consistent with the secondary study objective to evaluate the acceptability of tenofovir 1% gel when applied rectally, the following endpoint will be assessed:

- The proportion of participants who at their Final Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during receptive anal intercourse

Consistent with the secondary study objective to evaluate the safety of the placebo gel when applied rectally, the following endpoint be assessed:

- Grade 2 or higher adverse events in the placebo gel arm, as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and/or Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies) to this table

Consistent with the secondary study objectives to determine whether use of tenofovir 1% gel and use of 2% nonoxynol-9 gel (Gynol-II®) are associated with rectal mucosal damage, changes in the following endpoints will be assessed:

- Epithelial sloughing
- Intestinal histopathology
- Intestinal mucosal mononuclear cell phenotype
- Intestinal mucosal cytokine messenger RNA (mRNA)
- Intestinal mucosal gene expression arrays
- Cytokine profile in rectal secretions
- Fecal calprotectin
- Microflora

10.2.3 Exploratory Endpoints

Consistent with the exploratory objectives to determine whether regional heterogeneity exists between mucosal endpoints in samples collected at 9 cm and 15 cm for all parameters examined and to determine whether there is a correlation between histological abnormality and changes in mucosal biomarkers, changes in the following endpoints will be assessed:

- Epithelial sloughing
- Intestinal histopathology
- Intestinal mucosal mononuclear cell phenotype
- Intestinal mucosal cytokine messenger RNA (mRNA)
- Intestinal mucosal gene expression arrays
- Cytokine profile in rectal secretions

- Fecal calprotectin
- Microflora

10.3 Accrual, Randomization, Blinding, and Sample Size

The study will recruit a total of 60 RAI abstinent, HIV uninfected men and women from the three study sites. Within each study site, twenty participants will be enrolled and randomized to each of four study arms at a 1:1:1:1 ratio. Based on the prior studies with similar eligibility requirements, each site is expected to enroll 4 participants per month. Therefore accrual is anticipated to take approximately 5 months. The target for retention will be 95% of enrolled participants over the study period. To preserve the study power in the case of discontinuation/non-adherence, additional participants may enroll, at discretion of the protocol team, to replace participants who are discontinued or non-adherent to study product or scheduled study visits. Therefore the total sample size may be slightly exceeding 60 at the end of the study.

The SDMC will provide each study site with a series of numbered, sealed envelopes containing the randomization assignment for each participant. The envelopes will be assigned sequentially by site staff. Each participant will be assigned a product code number. Using a blinded list of product codes and assigned products, the pharmacist at each site will supply the study product. Multiple codes will be utilized to conceal and protect the randomization assignments in this study.

Throughout the period of study implementation and data analysis, neither study staff nor participants will be informed of the participants' random assignments. Study staff and participants will be unblinded after all study visits and data analyses are completed. As described in Section 9, if an investigator is concerned that a participant might be put at an undue risk by continuing product use, the investigator may discontinue the product use by this participant and document the discontinuation. In emergency situations, if a participant experiences an SAE that, in the opinion of the investigator requires unblinding to protect participant safety, the investigator will notify the PSRT to consider and rule upon the request.

For the proposed study sample size, the statistical properties of this study in assessing the safety of study products are summarized below. With 15 participants in each study arm, the probability of observing zero safety events, at least one safety event, and two or more safety events are listed in the following table assuming various true event rates. For instance, if the true rate of a safety endpoint is 5%, the probability of observing that endpoint in at least one participant out of 15 participants is 0.54. A higher true event rate will result in a larger probability to observe at least one event.

Table 17: Power Consideration for MTN-007

Event Rate	Pr(0 event/n=15)	Pr(≥ 1 event/n=15)	Pr(≥ 2 events/n=15)
1%	0.86	0.14	0.01
5%	0.46	0.54	0.17
10%	0.21	0.79	0.45
15%	0.09	0.91	0.68
25%	≤ 0.01	≥ 0.99	0.92

The statistical properties of this study may also be characterized by the width of the confidence intervals (CI) around observed event rate. The following table presents the exact 95% confidence intervals (Clopper-Pearson method) of the estimated rate when zero, one, or two endpoints are observed among 15 participants:

Table 18: Confidence Intervals

Number of Endpoints	Lower Bound of CI	Upper Bound of CI
0	0.0%	16.1%
1	0.1%	23.8%
2	1.2%	30.4%

Sample Size Consideration for Gene Expression Array Data

We performed a sample size calculation based on rough parameter estimates from existing Illumina array data, using the method by Lee and Whitmore.[99] Suppose there are 30,000 genes that are passing quality control/filtering and are anticipated not to be differentially expressed and suppose there are 1,000 probes that are differentially expressed. Assume the standard deviation of the difference between the $\log_2$ gene expression values across 2 participants is 0.71. We want to control the mean number of falsely positive gene expression changes to be less than 5. To detect a 2-fold change between the treatment and the control arm, we have a power of 0.61, 0.70 and 0.77 for a sample size of 8, 9 and 10 individuals per group, respectively. For comparisons between before and after treatment within the same individuals assuming the standard deviation of the differences of the $\log_2$ gene expression values before and after gel application is 0.4, and other parameters remain the same, the power of detecting a 2-fold change by a paired *t*-test will be approaching 1 for a sample size of 8. These power estimates are approximate, because the standard deviation varies across genes and because we do not know how many genes are actually not differentially expressed.

10.4 Data Analysis

Descriptive statistics and graphics will be used to summarize the characteristics of endpoints among three treatment-randomized groups. For categorical variables, the numbers and the proportions will be tabulated; for continuous variables, the mean, median, standard deviation, and quartiles will be reported. To assess the change of an endpoint from baseline to post-visit levels within a treatment arm, McNemar's test (for categorical variables) or paired *t*-test (for continuous variables) will be used. To assess the difference of certain endpoints after a treatment phase across treatment arms, Chi-square tests will be used for categorical variables with exact *P*-values if the expected

cell count in some stratum is small; *t*-test or linear regression will be used for continuous variables; nonparametric methods such as Wilcoxon rank-sum test may be used if sample size is small and data are non-normal. Generalized linear models will be used to regress continuous or categorical response variables on treatment arm, with or without adjusting for important baseline predictors. The longitudinal data combining endpoints measured at two treatment phases will be analyzed using generalized estimation equations (GEE) with robust variance estimates.

Baseline characteristics will be tabulated for three arms to check any imbalance of randomization. Due to small sample size, formal comparison will not be performed.

10.4.1 Primary and Secondary Analysis on Safety of Tenofovir 1% Gel and Placebo Gel

For the primary safety analysis, we will use per-protocol or modified intention to treat analysis based on the participants who have completed the baseline visit and at least one of two treatment visits. The rationale is that 1) the primary objective of this study is to evaluate the safety of study products. Adverse effects could only be induced by actual exposure to the study products. 2) Due to the small sample size being planned, any missing data generated from discontinuation/non-adherence can be a serious threat to the study power. Therefore we consider replacing participants who are discontinued /non-adherent. The number and the frequency of ≥ Grade 2 adverse events will be tabulated by study arm and treatment visit. Additional safety analyses will also tabulate the number and type of AEs observed overall, and by severity, site, and study arm. AEs that lead to discontinuation of product use and/or study participation will be tabulated separately. At each treatment visit, the rate of safety events will be compared to the baseline within the same treatment arms using McNemar's test, and the event rate will also be compared across treatment arms by Chi-square test. The logistic regression will be used to assess the difference of event rates across arms adjusting for baseline predictors.

10.4.2 Secondary Analysis on Acceptability

Consistent with the secondary study objective to evaluate the acceptability of tenofovir 1% gel when applied rectally, the secondary endpoint is to examine the proportion of participants who at their Final Clinic Visit report in the Product Acceptability Questionnaire that they would be very likely to use the candidate microbicide during receptive anal intercourse. We will calculate the proportion of participants who report high intentionality, operationalized as having a rating in the upper one third of the 10-point Likert scale, to use the product in the future every time they have receptive anal intercourse and compare proportions by study arm using a Chi-square test with exact p-values. Furthermore, we will examine intentionality to use the study gel on occasions when they do not use condoms or if they had to wait 30 minutes after application before having receptive anal intercourse with various types of partners (e.g., lovers, one-night stands, or other partners).

Additionally, to address the secondary study objective, we will conduct non-parametric tests (Kruskal-Wallis non-parametric test), if data are non-normal and sample sizes are unequal across the three conditions, to evaluate whether acceptability assessed at the Final Clinic Visit in the Product Acceptability Questionnaire is different by study condition. Because of insufficient statistical power to detect small or medium differences and the need to be aware of any trends, we will examine the distributions of each acceptability variable by treatment condition. Furthermore, we will inspect effect sizes to estimate how much variance in our measure of acceptability is accounted by the treatment arms. Although many of the individuals who voluntarily enroll in a study like this one would be predisposed to like a product (as measured at baseline by the microbicide intentions scale), the quantitative data will provide descriptive statistics of acceptability after they have had the chance to use the study product for seven days, specifically about the product's characteristics, application process, applicator, as well as the degree to which participants were bothered by leakage, soiling, or other problems related to gel use.

10.4.3 Secondary Analysis on the Mucosal Damage by Tenofovir 1% Gel and 2% Nonoxynol-9 Gel

The association of six sets of mucosal parameters with study products will be examined. Among them epithelial sloughing and histopathology are categorical measures, whereas the mucosal mononuclear cell phenotype, mucosal cytokine profile, weck cell cytokine and fecal calprotectin are continuous measures. All six parameters are measured at baseline, after the Treatment 1 Visit and at the Final Clinic Visit.

Statistical analyses will be first performed to establish the potential immunological biomarkers on microbicide safety in the N-9 gel arm. It is known that the N-9 gel will impose transient inflammation to rectal mucus. Therefore the mucosal parameters, namely various histology measures, cytokines, cell phenotypes or calprotectins, will be compared in biopsies sampled before and after the N-9 single-dose or seven-dose administration. The control arm without gel use will be included in this analysis to adjust for the within-subject fluctuation of these mucosal parameters across 3 sampling time-points. In particular, two sample *t*-test (Wilcoxon rank-sum test if skewed data) will be used to compare the differences of each individual parameter before and after gel use to those of the control arm. Longitudinal data modeling (GEE method) combining all three sampling time-points in both the N-9 arm and the placebo arm will be used to evaluate the differences of biomarkers induced by the N-9 application. Despite the randomization, the imbalance of baseline predictors could occur due to small sample size, additional regression analysis will be performed adjusting for other baseline demographic factors. Those markers that are significantly associated with the N-9 application will be considered as candidate mucosal parameters.

For the tenofovir and placebo gel arms, we will also evaluate the mucosal parameters before and after the gel application, using similar statistical methods as above. If there are mucosal parameters that are changed upon microbicide gel use, these parameters will be candidate markers for mucosal damage; however if there are no difference

detected, we will determine whether there is no mucosal damage or the parameter is not a good marker of mucosal damage by an inspection of results of this parameter from the N-9 arm.

10.4.4 Statistical Analysis of Gene Expression Array Data

We will perform our first statistical analysis once data from the 9 cm biopsies (9 cm up the rectum) will have been collected for a random subset of 8 participants in each group (placebo, tenofovir, N-9 gel, and no treatment), and for the three time points (0 hr, 30 min, 7 days). Microarray raw data will be imported to Beadstudio (v3.2, Illumina) for hybridization quality assessment. Data passing this quality control step will be exported to the *lumi* bioconductor package (www.bioconductor.org) for preprocessing, variance stabilization and normalization.[100, 101] In addition, probes displaying low variability across arrays will be filtered out. Significance analysis of differential expression will be performed by the LIMMA package in the Bioconductor software.[102] The comparison will be made between the 0 hr (baseline) and 30 min or 7 days of tenofovir, N-9, and placebo samples, and between treatment arms and the no treatment arm to identify genes responding differently to the three different compounds. *P*-values and false discovery rates (FDR) will be computed to assess the significance of differential expression. Differentially expressed genes will be defined as those for which the FDR is lower than a cut-off, for example 0.01, and for which the change between baseline and 30 min or 7 days of tenofovir, N-9, or placebo samples is larger than 2-fold or less than 0.5-fold.

Clustering analysis will be performed for the set of genes that show differential expression as identified by the significance analysis. Unsupervised learning methods will be used to identify genes with similar expression patterns. The number of clusters around center points, called centroids, will be determined empirically and the similarity of genes in each cluster will be computed by Euclidean distance. Supervised pattern search will be used to identify genes that share similar or inverse expression patterns to those of a reference gene (also called a profile search). Reference genes will be chosen from the list of biomarkers measured by the RT-PCR and Luminex® assays, based on concordance of expression changes induced by tenofovir, N-9, or placebo exposure between these assays and the microarrays. We may choose additional reference genes, based on findings using the unsupervised learning methods above.

10.4.5 Exploratory Analyses on Regional Heterogeneity of Mucosal Endpoints and Correlation between Histological Abnormality and Changes in Mucosal Biomarkers

To determine whether regional heterogeneity exists between mucosal endpoints, the mucosal parameters will be first compared between samples from 9 cm and 15 cm at each time point, using McNemar's test if the parameter is categorical, paired *t*-test (Wilcoxon signed-rank test if skewed data) if the parameter is continuous. Mixed-effect ANOVA models will be used to evaluate the heterogeneity of two sites across time with subject level modeled as a random effect. Additional analyses will be performed to

evaluate the correlation between mucosal biomarkers and histological abnormality across arms and three time points. At each time point, various cytokines, cell phenotypes or calprotectins will be compared between groups with different levels of histological abnormality, defined by sloughing or histopathology. Longitudinal data modeling (GEE method) combining three time points will be employed to evaluate the collected association of biomarkers with mucosal damage over the study period.

10.4.6 Analysis on Behavioral and Product Adherence Questionnaire

Data collected using the Baseline Behavioral Questionnaire will be primarily descriptive on demographic variables, such as ethnic background, age, education, income; sexual behavior in the prior three months; behavioral practices, such as lubricant and enema use; frequency of HIV testing; and substance use in the prior three months. We will also explore associations between pre-existing practices (i.e., lubricant use) and willingness to use a microbicidal gel.

Product adherence data as tallied by the Phone Reporting System will be analyzed using repeated measures logistic regression to compare gel-use rates (the proportion of outpatient doses used of the seven, once-daily doses prescribed) between treatment arms. GEE will be used to adjust for the within-subject correlations for repeated measures.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study case report forms will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all case report forms to be used as source documents. Data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://www3.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/PDF/SourceDocPolicy.pdf).

Each investigator will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with US regulations, for each of the three investigational products tested, the investigator will retain all study records for at least two years following the date of marketing approval for the study product for the

indication in which it was studied. If no marketing application is to be filed or if the application is not approved, the records must be retained until two years after the investigation is discontinued and the US FDA is notified.

Study records must be maintained on site for the entire period of study implementation. Thereafter, instructions for record storage will be provided by CONRAD. No study records may be moved to an off-site location or destroyed prior to receiving approval from both DAIDS and CONRAD.

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures for MTN-007 in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites available at: (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/QMPPolicy.pdf).

11.4 Study Coordination

CONRAD holds the IND applications for this study. Copies of all regulatory documents submitted to this IND by CONRAD are forwarded to DAIDS, for cross-referencing with other INDs for the study products. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement (CTA) executed by DAIDS and CONRAD.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chairs and DAIDS Medical Officer. Study implementation will also be guided by a common study-specific procedures manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN CORE, SDMC, NL and other designated members of the Protocol Team.

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The PSRT will address issues related to participant eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team as well as the MTN SMC.

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by Pharmaceutical Product Development Inc., (PPD) (Wilmington, NC) in accordance with Requirements for On-Site Monitoring of DAIDS Funded and/or Sponsored Clinical Trials available at: (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/OnsiteMonitor_Reqs.pdf).

Study monitors will visit the site to do the following:

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including US Code of Federal Regulations (CFR) Title 45 Part 46 and Title 21 Parts 50, 56, and 312
- Perform source document verification to ensure the accuracy and completeness of study data
- Verify proper collection and storage of biological specimens
- Verify proper storage, dispensing, and accountability of investigational study products
- Assess implementation and documentation of internal site quality management procedures
- Assess site staff training needs

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, SDMC, NL, CONRAD, NIAID, 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 to participants. Volunteers and study staff members will take part in a thorough informed consent process. 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, CONRAD, 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 site-specific informed consent documents and study-related documents (such as participant education and recruitment materials) are reviewed by an

Institutional Review Board (IRB) responsible for oversight of research conducted at the study sites. Any amendments to the protocol must be approved by the responsible IRB and DAIDS prior to implementation.

Subsequent to the initial review and approval, the responsible IRBs must review the study at least annually. Each investigator will make safety and progress reports to the IRBs at least annually and within three months after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. In addition, the results of all SMC reviews of the study will be provided to the IRBs. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Policy and Procedures Manual.

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) *WILL NOT* be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files. For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

13.3 Risk-Benefit Statement

13.3.1 Risks

General

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Disclosure of STI status may cause sadness or depression in volunteers. Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions.

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Participants in sites requiring partner notification in response to diagnosed STIs or HIV infection could have problems in their relationships with their sexual partners. Participants also could have problems in their partner relationships associated with use or attempted use of study products. In addition, participants could misunderstand the current experimental status of the study gels (i.e., their unknown safety and unproven efficacy) and as a result increase their HIV risk behaviors while in the study.

Data on participant risk behaviors and the occurrence of other potential social harms are collected from all participants on a quarterly basis. The Protocol Team monitors trends in risk behaviors over time based on these data, as well as the occurrence of other potential social harms, and takes any required follow-up action. This information also is reported to the SMC.

Participants will also be counseled on the importance of remaining RAI abstinent throughout the duration of the study to minimize risk to the rectum given the use of N-9 in this study combined with the unknown effects of the other study gels on the rectum.

Anoscopy

Anoscopy is a commonly practiced medical procedure and the procedures done in this trial will not involve any unusual risks or discomforts. The risk associated with these procedures is a small amount of bleeding. The biopsies are painless and heal quickly within 3 to 5 days. On extremely rare occasions, biopsies may lead to pain, bleeding or perforation of the gastrointestinal tract, or infection. Perforation occurs approximately less than once out of every 1,000 procedures. If this extremely rare complication occurs, antibiotics and surgery to repair the tear may be necessary.

Flexible Sigmoidoscopy

Flexible sigmoidoscopy is a commonly practiced medical procedure and the endoscopic procedures done in this trial will not involve any unusual risks or discomforts. The risks

associated with these procedures include mild discomfort and the feeling of having a "bloated stomach". Endoscopic biopsies are painless and heal quickly within 3 days. On extremely rare occasions, the endoscopic procedure or biopsies may lead to pain, infection (sepsis), bleeding or perforation of the gastrointestinal tract. Perforation occurs approximately once out of every 1,000 procedures. If this extremely rare complication occurs, antibiotics and surgery to repair the tear may be necessary.

Rectal Swabs and Sponges
There is the risk of mild discomfort from both these procedures in addition to a slight risk of bleeding.

Enemas
The main risk from having an enema is temporary discomfort. A hollow tube about the thickness of a pencil will be used to put approximately 120 mL of Normosol-R pH 7.4 into the rectum and flush it out again (a larger volume may be required if the initial volume does not produce results), along with any stool that is there. This may cause a "bloated" or "cramping" feeling. Some air may be pumped into the rectum as well, causing flatulence. The tube is small, but it might cause some anal or rectal discomfort if the subject has any hemorrhoids or other painful conditions.

Applicator
Use of a vaginal applicator to deliver a vaginal microbicide into the rectal compartment may be associated with minor anorectal trauma including lacerations and bruising in the anorectal area.

Tenofovir 1% Gel
There is currently no rectal safety data regarding the use of tenofovir 1% gel. Administration of tenofovir gel intravaginally at 0.3% and 1% concentrations in the HPTN 050 Phase 1 study resulted in minimal local irritation and little or no systemic adverse effects were identified.[76] Although 92% of participants reported at least 1 AE, 87% of those reported AEs were mild, and 70% of the AEs were limited to the genitourinary tract. Four severe AEs were reported, with only one, lower abdominal pain, thought to be product-related. The risks associated with tenofovir gel are believed to be less than those identified for systemic use. In the HPTN 050 Phase 1 study of tenofovir gel, serum PK analysis in a subset of participants demonstrated that there is no clinically significant systemic toxicity. Fourteen of 24 women with PK results had low, but detectable, serum tenofovir levels.

Given that Phase 1 data demonstrates measurable plasma concentrations of tenofovir in some participants, participants with hepatitis B infection might be at risk for development of tenofovir resistant hepatitis B. However, participants with known hepatitis B infection will not be eligible for enrollment. It is not known what effect tenofovir gel could have on the HIV virus or HIV disease progression in HIV infected participants or their partners. There is a theoretical risk that tenofovir absorbed systemically from vaginal tenofovir gel could result in mutations of the HIV virus in participants who become infected with HIV during the study, or their partner, if the

partner is infected with HIV. Limited resistance data from HPTN 050 show no new resistance mutations in plasma or cervicovaginal lavage specimens after 14 days of tenofovir gel use. No participant had high level tenofovir mutations (e.g., K65R).

Some of the possible side effects of the study gel are dryness, itching, burning, or pain in the genital area.

In the male tolerance study of tenofovir 1% gel, there were few genital findings observed after product use and all findings were classified as mild, were small in size and required no treatment.[78] The most common symptoms included mild pain (burning, irritation, discomfort) and pruritus. All reported urogenital symptoms were felt to be mild.

2% Nonoxynol-9 Gel

As evidenced by several safety and dose escalation studies involving vaginally administered N-9[81, 82, 84, 86], N-9 oftentimes resulted in greater reports of genital irritation and evidence of vaginal inflammation. In light of evidence that N-9 can possibly increase the risk of HIV acquisition, participants will not only be informed about the possible side-effects of N-9, they will be counseled on the importance of remaining RAI abstinent throughout the course of the study.

While N-9 is demonstrated to cause acute and rapidly healing mucosal injury such as epithelial separation from underlying basement membrane, only one study has addressed participant symptom perception during N-9 use. In this safety and toxicity study of rectal application of N-9, participants reported symptoms of rectal fullness that were often mild and transient. The majority of receptive partners in this study reported feelings of anorectal discomfort characterized by burning, itching, and pain. Rectal bleeding was reported by 29% of the receptive participants.[14] Urinary or penile symptoms in insertive partners were reported by 18 (51%) insertive partners during 6 weeks of product use and by four (12%) participants during the week of placebo use. Genital examination identified a meatal ulceration in an HIV-negative participant 3 days after once-daily N-9 gel use. The ulceration was HSV culture negative and resolved within 3 days off gel.

Symptoms were commonly reported during N-9 and placebo use. Relatively more symptoms were reported during N-9 gel use and at increased frequencies of N-9 gel use even after taking into account that N-9 gel was applied for a longer period of time (6 weeks) than placebo gel (1 week). However, when compared to the brief exposure to placebo in the first week, no specific symptom, stratified by HIV status, was more common during the weeks of N-9 use. Despite these symptoms, study retention was extremely high and 98% of participants completed the 6-week study.

Placebo Gel

There is currently no rectal safety data regarding the use of placebo gel. Twice daily intravaginal administration of placebo gel over the course of two weeks resulted in mild genital irritation, including genital burning, soreness, and pelvic pain, in 2 out of 14

women (14.3%).[48,88] Three out of the 14 women (12.4%) had colposcopic findings which included erythema, petechiae and peeling, although no findings with deep disruption were observed during follow-up. The placebo gel did not appear to alter vaginal health or shift vaginal flora and no SAEs were reported.

13.3.2 Benefits

Participants in this study may experience no direct benefit. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of safe and effective interventions to prevent HIV transmission. Participants also may appreciate the benefit of earlier diagnosis of STIs in addition to the opportunity to contribute to the field of HIV prevention research. Additionally, participants will be referred for treatment for any incidental findings detected during screening and other examinations.

13.4 Informed Consent Process

Written informed consent will be obtained from each study participant prior to both screening and enrollment. Written informed consent also will be obtained for long-term specimen storage and possible future testing, although consent for specimen storage is not required for study participation. In obtaining and documenting informed consent, the investigators and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials available at: (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/SourceDocPolicy.pdf).

Participants will be provided with copies of the informed consent forms if they are willing to receive them. Each study site is responsible for developing study informed consent forms for local use, based on the templates in the Appendices that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process specifically will address the following topics of import to this study:

- The unknown safety and unproven efficacy of the study products
- The need to practice safer sex behaviors regardless of study treatment group
- The importance of participants in all four study groups to the success of the study
- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)

- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The real yet limited benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

The informed consent process will include an assessment of each potential participant's understanding prior to enrollment and randomization of concepts identified by the protocol team as essential to the informed consent decision. Participants who are not able to demonstrate adequate understanding of key concepts after exhaustive educational efforts will not be enrolled in the study.

13.5 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by:

- Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), the US Office for Human Research Protections (OHRP), NIH, and/or contractors of the NIH
- Representatives of CONRAD
- Representatives of the MTN CORE, SDMC, and NL
- Site IRBs

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

Women who test positive for pregnancy at screening or enrollment visits will not be eligible to participate in this study.

A urine pregnancy test will be performed on all women at all clinic visits, and additionally if clinically indicated; investigators will discontinue study product among participants who test positive for pregnancy. During the informed consent process, women will be informed that none of the study products are methods of contraception and that the effects of these products on a developing human fetus are unknown.

13.6.2 Children

The NIH has mandated that children be included in research trials when appropriate. 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." This study does not plan to enroll children under 18 years old.

13.7 Compensation

Pending IRB approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits, child care, and time away from work.

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

13.9.1 HIV Counseling and Testing

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV testing time point. Testing will be performed in accordance with the algorithm in Appendix II. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will emphasize the unknown efficacy of the study products in preventing HIV infection. In accordance with the policies of the US NIH, participants must receive their HIV test results to take part in this study.

13.9.2 Care for Participants Identified as HIV-Infected

Participants will be provided with their HIV test results in the context of post-test counseling. Participants found to be HIV-infected will be referred to available sources of medical and psychosocial care and support, and local research studies for HIV-infected adults.

13.10 Study Discontinuation

This study may be discontinued at any time by NIAID, the MTN, CONRAD, the US FDA, the OHRP, or site IRBs.

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies and a Clinical Trial Agreement (CTA) between CONRAD 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, and CONRAD, for review prior to submission.

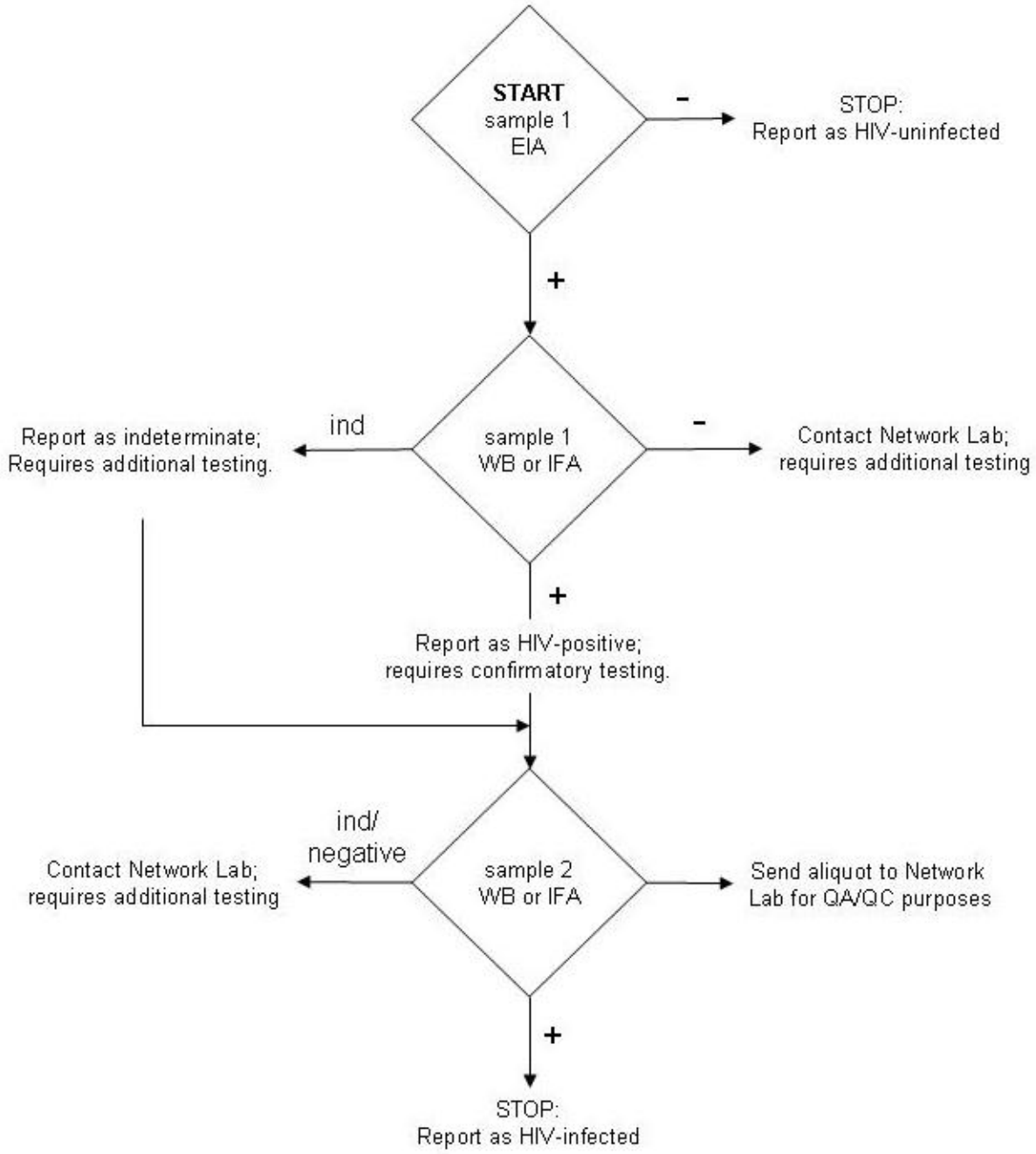
15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCR	ENR	TRTMT 1	F/U PHONE CALL	TRTMT 2	FINAL	F/U PHONE CALL	EARLY TERM.	INTERIM
Informed consents	X	X							
PTID	X								
Demographics	X								
Locator information	X	X	X		X	X		X	X
Test results		X	▲		▲	▲		▲	▲
Eligibility assessment/confirmation	X	X							
Randomization		X							
Reimbursement	X	X	X		X	X		X	
Schedule next study visit	▲	X	X		X				▲
Schedule follow-up phone assessment			X			X		▲	
Medical history	X	X	X		X	X		X	X
Menstrual history	♀	♀	♀		♀	♀		♀	♀
Concomitant meds	X	X	X		X	X		X	X
Physical exam	X	X	X		▲	X		X	▲
Rectal exam	X	X	X		▲	X		X	▲
Treat for RTIs/STIs/UTIs	▲	▲	▲		▲	▲		▲	▲
Document pre-existing conditions	X	X							
HIV pre-and-post test couns	X	▲				X		X	▲
HIV/STI risk reduction couns	X	X	X		X	X		X	X
Contraceptive couns	X	X	X		X				
Adherence couns (protocol and/or product use)		X	X		X				
Record/update AEs			X	X	X	X	X	X	▲
Baseline behavioral instructions and quest.		X							
Phone reporting system instructions*					X				
Product acceptability quest.*						X		X	
Qualitative hCG	♀	♀	♀		♀	♀		♀	♀
Dipstick UA	X					X		X	▲
Urine GC/CT by NAAT	X	▲	▲		▲	▲		▲	▲
CBC	X					X		X	▲
BUN, creatinine, ALT, AST	X					X		X	▲
Calculate creatinine clearance	X								
Syphilis RPR (confirm if necessary)	X	▲				X		X	▲
HIV-1 serology (confirm if necessary)	X	▲				X		X	▲
Plasma archive		X							
HBsAG	X								
HSV serology	X								
Rectal GC/CT by NAAT	X	▲	▲		▲	▲		▲	▲
Rectal microflora		X	X			X			
Rectal cytokines		X	X			X			
Normosol-R enema		X	X			X			
Rectal lavage,effluent, sloughing, and fecal calprotectin		X	X			X			
Anoscopy and biopsies		X	X		▲	X		▲	▲
Flex. sigmoidoscopy and biopsies		X	X			X		▲	▲
Condoms	X	X	X		X	X		X	X
Study gel and offer lubricant *			X		X				
Collect used & unused product*						X		X	▲

▲ If indicated; ♀ for females of childbearing potential; *for participants in treatment arms

APPENDIX II: HIV ANTIBODY TESTING ALGORITHM



APPENDIX III: TOXICITY TABLES

The AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009), Addendum 3 (Rectal Grading Table for Use in Microbicide Studies) will be the primary tool for grading adverse events for this protocol. Adverse events not included in that table will be graded by the DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009) or the DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009), Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies). In cases where an AE is covered in all three tables, Addendum 3 (Rectal Grading Table for Use in Microbicide Studies) will be the grading scale utilized.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December, 2004 (Clarification dated August 2009), is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

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

The current Manual for Expedited Reporting of Adverse Events to DAIDS is available at: http://rsc.tech-res.com/safetyandpharmacovigilance/.

APPENDIX V: HISTOPATHOLOGY SCORING SYSTEM

Participant ID: _____ **Visit No.: _____** **Visit Date: _____**

Biopsy Site: _____

Please Circle the Grade	Please Circle Subgrade	
Grade 0 No abnormality		
Grade 1 Mononuclear cell infiltrate	Low	High
Grade 2 Neutrophilic infiltrate lamina propria	Low	High
Grade 3 Neutrophilic infiltrate epithelium	Low *< 50% of crypts*	High *> 50% of crypts*
Grade 4 Crypt destruction	Low *probable*	High *unequivocal*
Grade 5 Erosion or ulceration	Low *Restitution, probable erosion*	High *Unequivocal erosion or ulceration*

APPENDIX VI: SAMPLE INFORMED CONSENT FORM (SCREENING)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIMH, US NIH

MTN-007
A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

Version 2.0
August 13, 2010

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study: Tenofovir Rectal Safety Study

INTRODUCTION

You are being asked to take part in these screening exams and tests for this research study because you are at least 18 years old, have had at least one experience of receptive anal sex in the past twelve months. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH) and CONRAD. The person in charge of the study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. The screening includes interview questions, urine and blood tests, a physical exam, and an examination of your rectum.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the screening tests that will be discussed with you. Once you understand the screening tests, and if you agree to take part, you will be asked to sign your name on this form. You will be offered a copy of this form to keep.

Before you learn about the screening tests, it is important that you know the following:

- You do not have to be in this study if you do not want to
- You may decide not to have the screening tests, or you may withdraw from the screening tests at anytime
- You are only being asked at this time to have the screening tests. Even if you agree to have the screening tests, you do not have to join the research study
- Some people may not be able to join the research study because of information found during the screening tests
- You will receive the results of the screening tests even if you are not eligible to join the study

WHY ARE THE SCREENING EXAMS AND TESTS BEING DONE?
These exams and tests are being done to see if you can join this study.

WHY IS THIS STUDY BEING DONE?
There are four main purposes of this study. The first is to find out whether the main study product, tenofovir gel, is safe when inserted into the rectum. We would also like to see if the other two gels used in this study are also safe when inserted into the rectum. Another main purpose of this study is to find out how men and women feel about inserting tenofovir gel into their rectum. Other studies are being done to see if the tenofovir gel, when inserted into the vagina, can be used to prevent the spread of Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS. Tenofovir gel is "experimental" for HIV prevention. This means **we do not know if it works to protect against HIV.** In future studies, we would like to see if tenofovir gel, when inserted into the rectum, can prevent the spread of HIV. In order to do that, we need to make sure that tenofovir is safe for use in the rectum, and understand how men and women feel about using the gel.

The side effects from tenofovir gel will be compared to the side effects of two other products: nonoxynol-9 (N-9) gel and placebo gel, as well as to participants who do not receive any of the study gels. N-9 gel is known to cause certain side effects and we want to make sure tenofovir gel does not cause the same side effects. The placebo gel does not have any medicine in it. Tenofovir gel and the placebo gel are not FDA approved for use in the rectum, and tenofovir gel has not been tested for rectal use in humans.

WHAT DO I HAVE TO DO IF I TAKE PART IN THE SCREENING EXAMS AND TESTS?
The screening visit will take about [sites to insert] hours. You will be asked to do the following things if you decide you want to join the study:

- Sign this form after you have read it or had it explained to you and had the chance to ask questions about the study
- Answer questions about yourself, such as where you live, your education, your behavior, including your sexual behavior, your medical history and any medicines that you may take and how we can contact you. Women will also be asked about menstrual cycle history
- Have a physical exam
- Have a rectal exam
- Learn about
    - different ways for women to avoid getting pregnant
    - how to avoid infections passed during sex
    - the meaning of your test results, including your HIV test results
    - how to use condoms
- Get treatment for any infections passed during sex or urinary tract infection that you may have, or learn from the study staff where you can get care or treatment

- Provide a urine sample to be tested for pregnancy (females) and urinary tract and sexually transmitted infections
- Have samples of fluid taken from your rectum to be tested for gonorrhea, chlamydia, and herpes
- Have a blood sample [sites to insert amount] taken to check the following:
    - the health of your blood, liver, and kidneys
    - HIV status
    - Syphilis status
    - Herpes status
- Receive condoms from the study staff
- It will take about [INSERT LENGTH OF TIME] to get the results of your screening tests. We will give you the test results when they are available.
- If the results of your screening tests and answers to the screening questions show you are able to take part in this study, the study staff will schedule an enrollment visit

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 US Food and Drug Administration (FDA), US National Institutes of Health (NIH), the MTN, the drug company supporting this study, the Office for Human Research Protections, 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
- Study staff believes that having the screening exams and tests would be harmful to you
- You do not want to learn 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 Rectal Exams:

- You may feel discomfort or pressure when your rectum is examined

Other Possible Risks:

- You may become embarrassed, worried, or nervous when discussing personal questions about your sexual behavior, ways to protect yourself 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 may have

We will make every effort to protect your privacy during the screening exams and tests. Your visits 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.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You may get no direct benefit from the screening exams and tests. However, you may benefit from the following:

- Physical exam and rectal exam
- Tests for sexually transmitted infections, rectal infections, and HIV (which may detect infections without obvious symptoms). If you have any of these infections, you will be referred for treatment if needed
- 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
- Counseling regarding safer sex and free condoms
- If your tests show 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 seek 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 care

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 with your doctor about these and other choices that may be available to you. The decision to not be in this study will not affect your care in any way.

WHAT ABOUT CONFIDENTIALITY?

This study is being conducted according to ethical guidelines. Efforts will be made to keep your personal information private. Your physical and rectal exams will be done in private. We cannot guarantee absolute confidentiality. In some situations, including emergencies, legal and professional rules may force us to share confidential information about you. If this study is published, your name will not be used and you will not be personally identified. You are encouraged but not required to tell sexual partners about your participation in this study.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), the US Office for Human Research Protections (OHRP), NIH, and/or contractors of the NIH
- [INSERT NAME OF SITE] IRB
- Study staff
- CONRAD (the company that supplies the gel used in this study)

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE*:*]
[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of those 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 should also 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].

In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you provide for study purposes. Even with the Certificate of Confidentiality, however, if study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the 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 the screening visit. You will receive [SITES TO INSERT - SPECIFIC AMOUNT OF MONEY] for the visit. You will also be paid for other costs to you for coming to the screening visit [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE].

WHAT HAPPENS IF I AM INJURED (EXPERIENCE HARM)?
If you are injured as a result of being in this study, the [INSTITUTION] will give you immediate treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. The US National Institutes of Health (NIH) does not have a program to provide money or other forms of compensation for your injuries. Signing this consent form does not change your legal rights.

[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 not to have the screening exams and tests any time. You will be treated the same no matter what you decide.

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, please inform let study staff.

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]

SIGNATURES
[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, please sign your name below.

_____	_____	
Participant Name (print)	Participant Signature	Date
_____	_____ _____	
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date

APPENDIX VII: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIMH, US NIH

MTN-007
A Phase I Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

Version 2.0
August 13, 2010

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study: Tenofovir Rectal Safety Study

INTRODUCTION

You are being asked to take part in these enrollment exams and tests for this research study because you are at least 18 years old, reported at least one experience of receptive anal sex in the past twelve months at the Screening Visit, and have passed the screening for this research study. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH) and CONRAD. 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 this study.

YOUR PARTICIPATION IS VOLUNTARY

This is an enrollment consent form and gives you information about the study. Study staff will talk with you about this information. You are encouraged to ask questions about the study at any time. If you agree to take part in this study, you will be asked to sign your name on this form. You will be offered a copy of this form to keep.

Before you learn about this study, it is important that you know the following:

- You do not have to join this study if you do not want to do so
- You may decide not to have the enrollment tests or you may withdraw from the enrollment tests at anytime
- Some people may not be able to join the research study because of information found during the enrollment process
- You will receive the results of your tests even if you are not eligible to join the research study

WHY IS THIS STUDY BEING DONE?

There are four main purposes of this study. The first is to find out whether the main study product, tenofovir gel, is safe when inserted into the rectum. We would also like

to see if the other two gels used in this study are also safe when inserted into the rectum. Another main purpose of this study is to find out how men and women feel about inserting tenofovir gel into their rectum. Other studies are being done to see if the tenofovir gel, when inserted into the vagina, can be used to prevent the spread of Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS. Tenofovir gel is "experimental" for HIV prevention. This means **we do not know if it works to protect against HIV.** In future studies, we would like to see if tenofovir gel, when inserted into the rectum, can prevent the spread of HIV. In order to do this, we need to make sure that tenofovir is safe for use in the rectum, and understand how men and women feel about using it.

The side effects from tenofovir gel will be compared to the side effects from two other products: nonoxynol-9 (N-9) gel and placebo gel as well as to the participants who do not receive any of the study gels. N-9 gel is known to cause certain side effects and we would like to make sure that tenofovir gel does not cause the same side effects as N-9. The placebo gel does not have any medicine in it. Tenofovir gel and the placebo gel are not FDA approved for use in the rectum, and tenofovir gel has not been tested for rectal use in humans.

STUDY GROUPS

There are four study groups. If you decide to take part in the study, you will be placed in one of the four groups: tenofovir gel, N-9 gel, placebo gel OR no gel. You will have a 1 in 4 chance of being in any one study group. There will be 15 participants assigned to each group for a total of 60 participants in the whole study. There are two different treatment periods for this study. At the first treatment period, if you are in one of the groups that receives a study gel, you will receive one dose of the study gel at that clinic visit. The second treatment period begins one week later. At that clinic visit, you will be given a 7-day supply of the same study gel as you received in your first treatment period. Your group will be chosen "by lot" [or other equivalent local term, for example, like flipping a coin or throwing dice] to be in one of these groups. You cannot choose your group, and the study staff cannot choose your group for you. Once you are in a group, you cannot change to another group. The study procedures will be the same for everyone participating in the study. The study staff and study doctor will not know what group you are in. All four of these groups are very important to the results of the study.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you decide to take part in this study, your first visit will continue today, after you read, discuss, understand, and sign this form. Study staff will help you understand the form and answer your questions before you sign this form.

Today, if you decide to participate and sign this form, you will find out which group you are in. You will answer questions about your sexual practices and will answer some questions about your medical history to make sure you are still eligible to join this study. Women will also be asked about menstrual cycle history. At today's visit, you will also:

- Have a blood sample [insert amount] taken in case there is a question about your lab results. After all testing is done, this sample will be destroyed according to the sites procedure for getting rid of blood samples that will not be needed after the end of the study
- Be asked to complete the informed consent document for the storage and future testing of specimens. You will only be asked to sign a separate consent document if you give your permission for the study staff to store your specimens for future testing

You will be in the study for about 4 to 11 weeks from the time of your Enrollment Visit (today) up until your follow-up phone call at the end of the study, and will use the study gel for a total of 8 days. Most of the visits will take [insert approximate amount of time]. Visits where study doctors will take small samples of tissue from your rectum will take [insert approximate amount of time].

At most visits, we will ask you to do the following:

- Let us know if there are any changes in where you live or how we may contact you
- Tell us about any changes in your medical or menstrual history
- Tell us if there have been changes to any medicines you are taking now
- Receive test results from previous visit, if available
- Have a physical exam
- Have an exam of your rectum
- Learn how to follow the rules of the study
- Learn about:
    - How to avoid infections that may be passed during sex, including HIV
    - How to avoid becoming pregnant
- If you are female, have your urine tested for pregnancy
- Receive condoms from the study staff

In addition, at the Enrollment, Treatment 1, and Final Visits, you will:

- Have an enema, which is a liquid injected into your rectum to promote a bowel movement. The liquid collected from your rectum afterwards will be tested to check the health of your rectum
- Have an examination of your rectum called anoscopy. This is when a short, hollow tube is placed inside your rectum to allow the study doctor to take a sample of rectal tissue
    - The doctor will take small tissue samples from near the opening of your rectum (biopsy). The tissue samples will be tested to check the health of your rectum
- Have an examination of your rectum (flexible sigmoidoscopy). This is when a flexible, long (a little longer than the anoscope) hollow tube is placed inside your rectum so that the study doctor can check the health of your rectum and take a sample of rectal tissue

- The doctor will take small tissue samples (biopsy) from further inside your rectum. The tissue samples will be tested to check the health of your rectum

Follow-Up Phone Call

This phone call will take place a day after the Treatment 1 Visit and will take about [Insert amount of time]. During this phone call, we will ask you to:

- Tell us about any side-effects you might have had from using the study gel

At the Treatment 1, Treatment 2 and Final Visits, you will:

- Be checked to see if the gel or biopsies caused any side-effects

At the Treatment 1 and Treatment 2 Visits, if you are in the group that receives the study gel, you will:

- Self-administer one dose of the study gel under the observation of study staff. You will also receive study lubricant to make it easier to insert the applicator. (Treatment 1 Visit)
- Receive a 7-day supply of study gel and study lubricant (this will be the same study gel that you received at the first treatment visit). (Treatment 2 Visit)
- Call an automated phone system each time you use the gel at home. You should insert the gel as close to the same time as possible, before your longest period of rest. When you call, you will be asked a brief set of questions. You will learn how the phone system works, and about the compensation you will receive for the calls. You will also have the opportunity to try the phone system out and ask any questions you may have. You may also be contacted by the study staff if you miss a phone call. (Treatment 2 Visit)

Final Visit

- If you are in the group that receives the study gel, answer questions about your experience using the study gel, including what you did and did not like about the gel
- Provide a urine sample to get tested for urinary tract infections
- Have a blood sample [insert amount] taken to:
  - Check the health of your blood, liver, and kidneys
  - Check for syphilis
  - Check for HIV
- You will be asked to return all used and unused applicators to the study clinic
- Schedule your follow-up telephone call

Follow-Up Phone Call

This phone call will take about [INSERT AMOUNT OF TIME]. During this phone call, we will ask you to:

- Tell us about any side-effects you might have had from using the study gel, if you are in the group that receives the study gel

At Any Time In The Study

If the study doctor thinks you have health problems that may be caused by infections, including those passed through sex, or if you have signs of infections, including those passed through sex, you may:

- Have a physical or rectal exam
- Give blood, urine, rectal fluid, or rectal tissue samples to test for infections
- Provide a urine sample for a pregnancy test (women)
- Get treatment or referrals for most types of infections if you need it

ARE THERE ANY RISKS AND/OR DISCOMFORTS?

Risks from Phlebotomy (blood tests)

- You may feel discomfort or pain when your blood is drawn
- You may feel dizzy or faint
- You may have a bruise, swelling, small clot, or infection where the needle goes in your arm or finger

RISK OF RECTAL EXAMS

- You may feel discomfort or pressure when your rectum is examined
- You may experience some discomfort when the swab or sponge is inserted into the rectum, and occasionally minor rectal bleeding may occur

Risks from Anoscopy and Flexible Sigmoidoscopy with Biopsies

- You may experience some mild discomfort and feel like you have a "bloated stomach"
- Even though the risk is low, you may experience infection, mild rectal irritation and may feel a sudden urge to have a bowel movement
- You may experience limited rectal bleeding (1 to 2 days after the procedure) related to the biopsies
- You may experience low blood pressure
- Even though the risk is very rare, there is a very small chance that you may have a hole or a tear in the intestine. This only happens once out of every 1,000 procedures. If this were to happen, surgery to repair the tear may be necessary. It is important that you do not put anything in your rectum for 7 days after the biopsies, because you may be at higher risk for getting or spreading an infection until the biopsy site(s) have healed

Risks from Enemas

- You may experience some mild discomfort and a bloated or cramping feeling

Risks from the Applicator

- You may experience some discomfort from the applicator since it has been designed for vaginal rather than rectal use

Risks from Tenofovir Gel
If you are in the group receiving tenofovir gel, the gel could cause some bad effects, which are described below. We do not yet know all the bad effects of tenofovir gel and we do not know what effects tenofovir gel will have on the rectum. Some, but not all, women who used the tenofovir gel in other studies have had:

- Dryness, itching, burning feeling, or pain in the genital area
- Vaginal candidiasis (a kind of vaginal infection)
- Discharge from the vagina
- Irritation in the genital area

Risks from N-9
If you are in a group that gets N-9 gel, the gel could cause some bad effects, which are described below. Many studies have been done to study the effects of N-9 gel, and show that when N-9 is used rectally, it can cause temporary damage to the lining of the rectum. Some men and women who used N-9 rectally in other studies have had:

- Burning, itching, or pain in the rectum
- Diarrhea or loose stools
- Rectal bleeding
- Enhanced transmission of HIV and other STIs

Risks from Placebo Gel
If you are in a group that gets placebo gel, the gel could cause some bad effects, which are described below. Some studies have been done to study the effects of placebo gel, and show that when it used vaginally, it can cause the following:

- Burning or soreness in the genital area
- Pain in the pelvic area

Pregnancy/Risks to Fetus
The effects of the study gels on the pregnancy or on baby's development are not known. It is for this reason that study staff will counsel you on ways to avoid becoming pregnant while you are in the study.

Other Possible Risks:

- You may become embarrassed, worried, or nervous when discussing personal questions about your sexual behavior, 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 study visits, exams, and tests. Reports to the automated phone system will be stored in computers that are password-protected and will not include personal information that could identify or link information to you. 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 or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your HIV status could also cause problems between you and your partner.
Some studies of HIV prevention have found an unexpected higher risk of study participants contracting HIV. This could happen in any study, including this study. Because of this, the study staff will remind you not to have receptive anal sex while participating in this study, and will also remind you of the importance of using condoms to protect against HIV.

WHAT ARE THE BENEFITS?

You may get no direct benefit from being in this study. **We do not know if tenofovir gel works to protect against HIV.** Also, you may not receive any gel and if you do, the gel you receive may be the N-9 or the placebo gel. Because of this, study staff will remind you of the importance of not having receptive anal sex during the study and will also remind you of the importance of using condoms to protect against HIV.

You or others may benefit in the future from information learned in this study. You may also get some personal satisfaction from being part of research on HIV prevention. This is true no matter what study group you are in.

You will have physical exams and rectal exams. You will have tests to check on the health of your blood, liver, and kidneys. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you.

You will get counseling and testing for HIV. You will receive free condoms. If you have infections passed through sex, other than HIV infection, you will be offered medicine to treat them, if needed. This study does not provide medication for treatment of HIV/AIDS. If you become infected with HIV, you will be referred for medical care, counseling, and other services available to you.

WHY MIGHT I HAVE TO STOP TAKING THE STUDY DRUG EARLY?

You may have to stop using gel if you:

- Become infected with HIV
- Become infected with hepatitis B
- Become pregnant
- Are breastfeeding
- Are taking certain medications that affect your kidneys
- Are unable or unwilling to follow study procedures or instructions
- Could be harmed by continuing to take gel

WHY MIGHT I BE WITHDRAWN FROM THE STUDY WITHOUT MY CONSENT?

You may be withdrawn from the study without your consent for the following reasons:

- The study is stopped or canceled
- Study staff feel that staying in the study would be harmful to you
- You are not willing to find out your HIV test results

- Other reasons, decided by the study staff

If you withdraw early from the study, we will ask you to come in for a final visit with all the exams and tests listed for the final visit, if the study doctor thinks the exams and tests need to be done.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?
You do not have to be in this study. The decision to not be in this study will not affect your care in any way

WHAT ARE THE COSTS TO ME?
There is no cost to you for the study procedures and exams.

WILL I RECEIVE ANY PAYMENT?
You will be paid for your time and effort for your scheduled study visits. You will receive [SITES TO INSERT - SPECIFIC AMOUNT OF MONEY] for each visit. You will also be paid for other costs to you for coming to your scheduled visits [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE].

During the Final Visit you will receive $2 for each call you made to the phone reporting system ($2 per day X 7 days = $14), plus $10 if you make a call every day during the 7 days that you used the study gel, for a total of up to $24.

WHAT ABOUT CONFIDENTIALITY?
This study is being conducted according to ethical guidelines. Efforts will be made to keep your personal information private. Your physical and rectal exams will be done in private. We cannot guarantee absolute confidentiality. In some situations, including emergencies, legal and professional rules may force us to share confidential information about you. If this study is published, your name will not be used and you will not be personally identified. You are encouraged but not required to tell sexual partners about your participation in this study.

Your records may be reviewed by:
- Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), the US Office for Human Research Protections (OHRP), NIH, and/or contractors of the NIH
- [INSERT NAME OF SITE] IRB
- Study staff
- CONRAD (the company that supplies the gels used in this study)

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE:]
[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of those 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 should also 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].

In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you provide for study purposes. Even with the Certificate of Confidentiality, however, if study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

WHAT HAPPENS IF I AM INJURED (EXPERIENCE HARM)?

[SITES TO SPECIFY INSTITUTIONAL POLICY] It is unlikely that you will be injured as a result of study participation. If you are injured, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in exams and tests is completely voluntary. You may choose not to have the exams and tests any time. You will be treated the same no matter what you decide.

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, please inform let study staff.

WHAT DO I DO IF I HAVE PROBLEMS OR QUESTIONS?

If you ever have any questions about the study, or if you have a research-related injury, you should contact [INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF] at [INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB or other organization appropriate for the site] at [insert physical address and telephone number].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or community advisory board (CAB) member [staff will decide which] at [insert physical address and telephone number].

[SITES THAT PREFER NOT TO INCLUDE THE TABLE OF STUDY VISITS AND EVALUATIONS ON THE FOLLOWING PAGE MAY DELETE THIS ATTACHMENT]

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, please sign your name below.

_____	_____	
Participant Name (print)	Participant Signature	Date
_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date

MTN-007 Schedule of Study Visits and Evaluations for Participants

	Screening	Enrollment	Treatment 1	Follow-up phone call	Treatment 2	Final	Follow-up phone call	Early Termination Visit
Informed consents	X	X						
Study identification number	X							
Information about where you live and how we can contact you	X	X	X		X	X		X
Questions to see if you can join the study	X	X						
Test results		X	▲		▲	▲		▲
Information about the study	X							
Information about your health and the medicines you are taking	X	X	X		X	X		X
Physical exam	X	X	X		▲	X		X
Rectal exam	X	X	X		▲	X		X
Questions about your health after you start using the study gel			X	X	X	X	X	X
HIV pre-and post-test counseling	X	▲				X		X
Learn about ways to avoid pregnancy	X	X	X		X			
Learn about ways to avoid getting infections passed through sex	X	X	X		X	X		X
Learn how to follow the rules of the study		X	X		X			
Baseline behavioral questionnaire		X						
Learn about the phone reporting system					X			
Answer questions about the study gel						X		X
Receive study gel			X		X			
Return used and/or unused applicators to the clinic						X		X
Laboratory Tests								
HIV and syphilis tests	X	▲				X		X
Test for herpes	X							
Test for hepatitis	X							
Tests for gonorrhea and chlamydia	X	▲	▲		▲	▲		▲
Blood tests	X	X				X		X
Urine sample for pregnancy test	♀	♀	♀		♀	♀		♀
Urine samples to check the health of your liver and kidneys	X					X		X
Enema		X	X			X		
Flexible sigmoidoscopy, anoscopy, and rectal tissue samples		X	X		▲	X		▲

X = required, ▲= if indicated, ♀=required for female participants

APPENDIX VIII: SAMPLE INFORMED CONSENT DOCUMENT (Storage and Future Testing of Specimens)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIMH, US NIH

MTN-007
A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

Version 2.0
August 13, 2010

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study: Tenofovir Rectal Safety Study

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 tissue, and/or fluid from your rectum 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 or make your mark on this consent form. You will be given a copy of this form to keep.

HOW WILL YOU GET THE SAMPLES FROM ME?

The research doctors want to save any extra tissue and/or rectal fluid leftover from your tests during the study. The leftover tissue samples and rectal fluid will be kept and used for future research.

HOW WILL YOU USE MY SAMPLES?

Your samples will be used to look for ways that your body responds to infection (such as cells, proteins, and other chemicals in your body). Tests may also include checking your genes (material passed from parent to child that determines the make-up of the body and mind), since they might affect how your body responds to disease. Your genes might make you more or less likely to get an infection, affect your responses to infection, or make your responses to treatment stronger or weaker. No other kinds of genetic test will be done on your stored samples 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 your medical care. 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 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 securely. The storage facilities are made so that only approved researchers will have access to the samples. 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 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?
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.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), the US Office for Human Research Protections (OHRP), NIH, and/or contractors of the NIH
- [INSERT NAME OF SITE] IRB
- Study staff
- CONRAD (the company that supplies the gels used in this study)

In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your

participation or information you provide for study purposes. Even with the Certificate of Confidentiality, however, if study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

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]

Please carefully read the statements below and think about your choice. No matter what you decide it will not affect your participation in the MTN-007 study or your medical care. Please initial or mark your choice and sign your name below.

____I agree to allow my leftover samples to be stored for future testing.

OR

____I do not agree to allow my leftover samples to be stored for future testing.

_____	_____	
Participant's Name (print)	Participant's Signature	Date
_____	_____	
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date

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Section 3. Documentation Requirements

Study staff are 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-007.

3.1 Essential Documents

The Division of AIDS (DAIDS) Standard Operating Procedure (SOP) for Essential Documents specifies the essential documents that study sites must maintain for DAIDS-sponsored studies, including MTN-007. The DAIDS SOP for Essential Documents can be found at:

http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/essentialdocpolicy.pdf.

Note: 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.

Table 3-1 presents a suggested essential documents filing structure for MTN-007. Study sites are not required to adopt the suggested structure, but are encouraged to consider it when developing their filing approach for MTN-007. 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 Table 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 ensure study integrity, 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 3.3, rather than Table 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 23-25 in Table 3-1). Other lab-related essential documents (e.g., lab SOPs) may be filed at the site laboratories.

- The suggested filing structure assumes that MTN-007 participant case history records will be stored separately from the other essential documents listed in Table 3-1. Section 3.2 below provides information on the required contents of those records. The suggested filing structure also assumes that the MTN-007 Screening and Enrollment Log and Participant Name-ID Number Link Log (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 Table 3-1.

3.2 Participant Case History Documentation

Study sites must maintain adequate and accurate participant case history records containing all information pertinent to MTN-007 for each study participant.

3.2.1 Case History Contents

Participant case histories for MTN-007 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.
- 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 deviations be documented in participant records, along with reasons for the departures and/or attempts to prevent or correct the departures, if applicable. Study site staff are also responsible for reporting deviations using the MTN Protocol Deviation Report Form, which is posted on the MTN Web site:

Site staff will submit a draft form within 30 calendar days of site awareness of the occurrence to the study management team for review and comments to ensure that the form is complete and accurate prior to broader distribution. Once the form is finalized, it should be distributed to an e-mail group designated for MTN-007 Protocol Deviations which includes the following: Protocol Chair, FHI Clinical Research Manager, SDMC Project Manager, NL representative, and the DAIDS Medical Officer.

3.2.2 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, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the trial).

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://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocpolicy.pdf .

The DAIDS SOP 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-007, it is expected that participant case history records will consist of the following source documents:

- Narrative chart notes
- Clinic randomization envelopes and prescriptions documenting participants' random assignments
- Pharmacy randomization envelopes, investigational product dispensing and chain of custody records (maintained in the study site pharmacy)
- Visit checklists and/or other site-specific flowsheets
- Local laboratory testing logs and result reports
- DataFax and Non-DataFax forms provided by the MTN Statistical and Data Management Center (SDMC)
- 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, Table 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 13 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 at which a contact takes place, or at which particular procedures take place, also should be specified when necessary to document adherence to protocol requirements. Chart notes also must be used to document the following:

- The screening, enrollment and specimen storage 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 departures 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.

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 13 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 Table 3-3 for a listing of all DataFax and non-DataFax forms to be provided for this study.

The SDMC will provide all forms in pre-assembled packets for each protocol-specified study visit (Screening Visit, Enrollment Visit, Treatment 1 Visit, etc.). Packets of other "as needed" forms also will be provided. The packets will be produced and shipped from the printing company to each study site.

As shown in Tables 3-4 and 3-5, many of the DataFax and non-DataFax forms provided by the SDMC have been designed to serve as source documents. Each study site must document 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 are not able to record data directly onto forms designated as source documents, 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

3.2.3 Document Organization

Study staff must make every effort to store all study records securely and confidentially. Case history records must be stored in the same manner for all participants, in areas with access limited to authorized study staff only. Study staff are 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. This documentation also must be available for reference should participants present to the site for re-screening. For participants who enroll in the study, screening documentation should be transferred into large ring binders that 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. 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 non-study site locations.

Per Section 13.5 of the MTN-007 Protocol, all study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to authorized study staff. Data collection process and administrative forms, laboratory specimens, and other reports will be identified by a coded number – PTID) only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. When in use, these documents should not be left unattended or otherwise accessible to study participants, other study clinic patients, or any other unauthorized persons. Participants' study information will not be released without their written permission, except as necessary for monitoring (see Section 12 of the MTN-007 Protocol).

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 resolving/troubleshooting CASI questionnaire issues (accessing questionnaires, problems with the computers, etc.)
- 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)
- 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)

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

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

- Current MTN-007 protocol
- Current Investigator's Brochures for Tenofovir 1% Vaginal Gel (Tenofovir Gel), HEC Placebo gel and the Package Insert for Nonoxynol-9 (if brochures and package insert are on file in the clinic essential document files and are not easily accessible to pharmacy staff)
- Current MTN-007 FDA Form 1572
- Current list of authorized prescribers and staff authorized to sign MTN-007 Study Product Prescriptions (names and signatures)
- Pharmacy Establishment Plan
- MTN-007 pharmacy Chain of Custody SOP
- MTN-007 Pharmacy Policy and Procedures Manual
- MTN-007 PTID list (provided by the MTN SDMC)
- MTN-007 product shipping and receipt documentation
- MTN-007 product storage temperature logs
- MTN-007 investigational agent accountability records
- MTN-007 participant-specific records (including prescriptions, dispensing records, and DataFax forms as applicable)
- MTN-007 monitoring visit reports
- MTN-007 communications with site clinic staff
- MTN-007 communications with MTN CORE Pharmacist
- MTN-007 communications with the MTN Coordinating and Operations Center (CORE)
- MTN007 communications with the MTN SDMC
- Other MTN-007 communications
- Other locally-required administrative, operational, and/or regulatory documentation

Pharmacy staff will document the receipt, dispensing, and final disposition of the investigational products used in the study, i.e., Tenofovir 1% Gel, HEC Placebo and 2% Nonoxynol-9. Separate accountability records must be maintained for each product, per instructions provided in the *MTN-007 Pharmacy Policy and Procedures Manual* available from the MTN Pharmacist.

Pharmacy staff also will maintain in the study pharmacies randomization materials for all enrolled study participants and product dispensing records for all participants, per instructions in the *MTN-007 Pharmacy Policy and Procedures Manual*. 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 3.2 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 study integrity, neither study clinic staff nor study participants 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 or other information related to participants' random assignment (see also Section 9.1 of this manual).

3.4 Record Retention Requirements

All study records must be maintained for at least two years after the investigation is discontinued and the US Food and Drug Administration (FDA) is notified. Study product records must be stored in the study pharmacies, with access limited to authorized study pharmacy staff only. DAIDS will provide further instructions for long-term storage of study records after the study is completed. No records are permitted to be relocated off site, discarded, or destroyed without prior written authorization from DAIDS and CONRAD.

Table 3-1
Suggested Filing Structure for MTN-007 Essential Documents

File/Binder #1: MTN-007 Protocol and Current Informed Consent Forms

1. MTN-007 Protocol (including copy of signed and dated protocol signature page): Version 2.0 and any subsequent protocol Clarification Memos, Letters of Amendment, and Amendments issued after Version 2.0
2. Currently-approved MTN-007 informed consent forms

File/Binder #2: Regulatory Authority Documentation (if applicable)

3. Regulatory Authority Correspondence/Authorization/Approval/Notification of Protocol (if more than one regulatory authority has oversight responsibility for research performed at the study site, include subsections for each authority)

File/Binder #3: IRB Documentation

4. FWA documentation for IRB
5. Roster of IRB (if available)
6. Relevant IRB Submission Requirements/Guidelines/SOPs
7. IRB Correspondence for IRB: File complete copies of all correspondence to and from the IRB; include all enclosures/attachments for all submissions, even if copies of the enclosures/attachments are filed elsewhere; include all approval documentation.

File/Binder #4: Product Safety Information

8. Investigator's Brochure for Tenofovir 1% Gel: current version and any subsequent updates
9. Investigator's Brochure for HEC Placebo gel: current version and any subsequent updates
10. Package Insert for Nonoxynol-9: current version and any subsequent updates
11. Product Safety Information/Reports/Memos

Notes:

- It is assumed that expedited adverse event reports will be stored in participant study notebooks.
- It is assumed that documentation of IRB submission of above-listed documents (if applicable) will be maintained in the relevant IRB Files/Binders (i.e., File/Binder #3).

File/Binder #5: MTN-007 Study-Specific Procedures (SSP) Manual

12. Final version 2.0 and any subsequent updates (when available)

Notes:

- 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.
- 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.

File/Binder #6: MTN-007 Study-Specific Standard Operating Procedures

13. Final approved version of each SOP, and any subsequent updates to each

File/Binder #7: MTN-007 Staffing Documentation

14. FDA Form 1572 (copy of original and dated form submitted to the RSC for Protocol Registration, and any subsequent updates)
15. MTN-007 Investigator of Record CV (copy of CV submitted to the RSC for Protocol Registration; ensure that the CV is current prior to initiating MTN-007; it is recommended that CVs be signed and dated to document at least annual updating)
16. Financial Disclosure Forms (original signed and dated forms, and any subsequent updates)
17. Study Staff Roster (submitted to MTN CORE (FHI) for study activation, and any subsequent updates)
18. Study Staff Identification and Signature Sheet (if not combined with staff roster; original and any subsequent updates)
19. Study Staff Delegation of Duties (if not combined with staff roster; original and all updates)
20. CVs for Study Staff other than the IoR (ensure that all CVs are current prior to initiating MTN-007; it is recommended that CVs be signed and dated to document at least annual updating)
21. Study Staff Job Descriptions
22. Documentation of Study Staff Training

Table 3-1
Suggested Filing Structure for MTN-007 Essential Documents

File/Binder #8: Local Laboratory Documentation 23. Local Laboratory Certification(s), Accreditation(s) and/or Validation(s): file documentation current at time of study activation and all subsequent updates 24. 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 25. Laboratory Manager CV (or cross-reference to CV contained in File/Binder #7) Note: • 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).
File/Binder #9: Monitoring Visit Documentation 26. Monitoring Visit Log 27. Initiation and Monitoring Visit Reports and Documentation of Response to Visit Findings
File/Binder #10: Documentation of Other MTN Site Visits 28. (Non-Monitoring) Site Visit Log 29. MTN CORE (FHI) Site Visit Reports and Documentation of Response to Visit Findings 30. MTN SDMC Site Visit Reports and Documentation of Response to Visit Findings 31. MTN Network Lab Site Visit Reports and Documentation of Response to Visit Findings 32. Other Site Visit Reports and Documentation of Response to Visit Findings
File/Binder #11: Study-Related Sponsor Communications 33. Study-Related Communications to and from DAIDS 34. Communications to and from DAIDS RSC (includes copies of all submissions to the DAIDS Protocol Registration Office, which will be prepared by the sites with copies provided to the MTN CORE, as well as the current monthly DAIDS IB/PI listing and year-end and current monthly DAIDS Comprehensive Safety Distribution Report) Notes: • Communications related to individual MTN-007 study participants will be filed in individual participant study records. • Product-related communications with MTN CORE Pharmacist will be stored in the study pharmacy.
File/Binder #12: Other Study-Related Communications 35. Study-Related Communications to and from MTN CORE 36. Study-Related Communications to and from MTN SDMC 37. Study-Related Communications to and from MTN Network Lab 38. Other Study-Related Communications Notes: • Communications related to individual MTN-007 study participants will be filed in individual participant study records. • Product-related communications with MTN CORE Pharmacist will be stored in the study pharmacy.
File/Binder #13: Study Site Staff Meeting Documentation 39. MTN-007 Staff Meeting Agendas, Participant Lists/Sign-In Sheets, and Summaries Note: • Meeting documentation should be filed beginning from the date of the MTN-007 Operational Walkthrough
File/Binder #14: Conference Call Documentation 40. MTN-007 Protocol Team Call Summaries 41. MTN-007 Community Working Group Conference Call Summaries 42. Summaries of Other MTN-007 Conference Calls including Operations Group Call Summaries Note: • Conference call summaries will be filed beginning from the date of the MTN-007 Protocol Development Call

Table 3-1
Suggested Filing Structure for MTN-007 Essential Documents

File/Binder #15: DAIDS and Other Reference Documentation
43. DAIDS SOP for Source Documentation (Version 2.0 and any subsequent updates)
44. DAIDS SOP for Essential Documents (Version 2.0 and any subsequent updates)
45. DAIDS Protocol Registration Policy and Procedures Manual (March 2010 and any subsequent updates)
46. Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010)
47. US Regulations Applicable to Conduct of MTN-007 (45 CFR 46; 21 CFR 50, 54, 56, and 312)
48. Any other relevant manuals or reference documents
File/Binder #16: Site-Specific Study Activation Documentation
49. Site-Specific Study Activation Documents

Table 3-2
Guide to Required Case History Elements and Source Documents for MTN-007

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.	Signed and dated informed consent forms; Demographics form, Locator form; Screening Consent form; Screening Eligibility form (non-DataFax); Enrollment Visit Eligibility form (non-DataFax); Medical Eligibility form (non-DataFax); Laboratory Results form; STI Laboratory Results form; HIV Test Results form; Baseline Medical and Menstrual History form (non-DataFax), Concomitant Medications Log form, Physical Exam form (non-DataFax), Pre-existing Conditions form; local lab logs and result reports[§]; signed and dated chart notes.
A record of the participant's random assignment.	Clinic randomization envelope; Pharmacy randomization envelope; Clinic randomization tracking record; Pharmacy randomization tracking record; study product prescription; participant-specific pharmacy dispensing record(s)
A record of the participant's exposure to the investigational study products.	Study product prescription, participant-specific pharmacy dispensing record(s); study product returns documentation; study product request slip; dispensed product 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.
Information on the participant's condition before, during, and after the study.	All documents listed above; Enrollment form; Follow-up Visit/Phone Call form; Follow-up Medical and Menstrual History form (non-DataFax); Rectal Exam form; Anoscopy and Sigmoidoscopy Results form; Adverse Experience Log form; Product Hold/Discontinuation Log form; Pregnancy Report and History form; Pregnancy Outcome form; Interim Visit form; Missed Visit form; Participant Transfer form; Participant Receipt form; Termination 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.

*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.

Table 3-3
MTN-007 DataFax and Non-DataFax Forms

MTN 007 DataFax Forms	MTN 007 Non-DataFax Forms
Adverse Experience Log	MTN 007 LDMS Specimen Tracking Sheet
Anoscopy and Sigmoidoscopy Results	Medical Eligibility
Concomitant Medications Log	Participant-reported Baseline Medical and Menstrual History
Demographics	Participant-reported Follow-up Medical and Menstrual History
End of Study Inventory	Physical Exam
Enrollment	Screening Visit Eligibility
Follow-up Visit/Phone Call	Enrollment Visit Eligibility
HIV Test Results	
Interim Visit	
Laboratory Results	
Missed Visit	
Participant Receipt	
Participant Transfer	
Pre-Existing Conditions	
Pregnancy Outcome	
Pregnancy Report and History	
Product Hold/Discontinuation Log	
Rectal Exam	
Screening Consent	
Specimen Storage	
STI Laboratory Results	
Study Product Returns	
Termination	

Table 3-4
Use of MTN-007 DataFax Forms as Source Documents
(Forms listed in alphabetical order)

Form Name	Acronym	Is Form Source?	Comments
Adverse Experience Log	AE-1	Yes	Form and/or participant chart notes may be source for all items.
Anoscopy and Sigmoidoscopy Results	ASR-1	Yes	Form is source for all items. Supplemental information will be recorded in the participant chart notes.
Concomitant Medications	CM-1	Yes	Form is source for all items.
Demographics	DM-1-2	Yes)	Form is source for all items, since participant responses are recorded directly onto the form.
End of Study Inventory	ESI-1	No	All items are based on source data recorded on other documents.
Enrollment	ENR-1	Mixed	A participant's chart notes, Baseline Medical and Menstrual History form, Screening Visit Eligibility form, and/or Medical Eligibility form is source for item 1. The Enrollment Informed Consent form is source for item 2. The Specimen Storage Informed Consent form is source for items 3 and 3a. The Clinic Randomization Envelope Tracking Record is source for items 4-6. The Enrollment Visit checklist is source for items 7 and 7a.
Follow-up Visit/Phone Call	FU-1	No	All items are based on source data recorded on other forms.
HIV Test Results	HTR-1	Mixed	Local laboratory report(s) are source for items 1-2. Form may be source for item 3.
Interim Visit	IV-1	Mixed	Form may be source for item 1. Form is source for item 2. Local laboratory reports/logs are source for item 3a.
Laboratory Results	LR-1	No	Local laboratory reports are source for all items.
Missed Visit	MV-1	Yes	Form may be source for all items. Supplemental information will be recorded in participant chart notes.
Participant Receipt	PRC-1	No	Participant Transfer form is source for items 1-2. Informed Consent forms are source for items 3-4a.
Participant Transfer	PT-1	Yes	Form is source for all items.
Pre-Existing Conditions	PRE-1	No	All items are based on source data recorded on the non-DataFax Participant-reported Baseline Medical and Menstrual History form, non-DataFax Physical Exam form, Rectal Exam form, Anoscopy and Sigmoidoscopy form, and/or participant chart notes.
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. If medical records are obtained, then they will be source for as many items as possible.

Form Name	Acronym	Is Form Source?	Comments
Pregnancy Report and History	PR-1	Mixed	Form is source for item 2-3. All other items are based on source data recorded on the non-DataFax Participant- reported Baseline Medical and Menstrual History form ("Women Only" pages) and the non-DataFax Participant-reported Follow-up Medical and Menstrual History form ("Women Only" pages).
Product Hold Discontinuation	PH-1	Yes	Form is source for all items. Supplemental information may be captured on the PR-1 form, SLR-1, HTR-1 form, and/or AE Log form, depending on the reason for the permanent discontinuation.
Rectal Exam	RE-1	Yes	Form is source for all items. Supplemental information is recorded in the participant chart notes.
Screening Consent	SC-1	No	The source document for item 1 is the Demographics form. The source document for items 2-2a is the screening informed consent form.
Specimen Storage	SS-1	No	Visit checklists and/or participant chart notes will serve as source for all items.
STI Laboratory Results	STI-1	No	Local laboratory reports will serve as source for all items.
Study Product Returns	SPR-1	Yes	Form is source for all items.
Termination	TM-1	No	All items are based on source data recorded on other documents.

Appendix 1 Part C
MTN-007 Non-DataFax Forms Used as Source Documents
(Forms listed in alphabetical order)

Form Name	**Is form source?**	Comments
MTN 007 LDMS Specimen Tracking Sheet	No	Visit checklists and participant chart notes are source for all items.
Medical Eligibility	No	All items are based on source data recorded on other source documents
Participant-reported Baseline Medical and Menstrual History	Yes	Form is source for all items though may be supplemented with other source documents as needed (i.e. medical records).
Participant-reported Follow-up Medical and Menstrual History	Yes	Form is source for all items though may be supplemented with other source documents as needed (i.e. medical records).
Physical Exam	Yes	Form is source for all items.
Screening Visit Eligibility	Mixed	Form is source for items 1-16, as these items are interviewer-administered. The local participant locator form is source for item 17. Local laboratory pregnancy test log report is source for item 18.
Enrollment Visit Eligibility	Mixed	Form is source for item 1. The Participant-Reported Baseline Medical and Menstrual History form is source for item 2.

Section 4. Participant Accrual

This section covers general guidelines for accrual and recruitment methods at the site. Additional information regarding participant accrual can be found in the MTN-007 Protocol, section 10.3.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

Each site will enroll approximately 20 participants for a total of 60. The accrual process should be completed in approximately 5 months or at a rate of about 4 participants per month per site until the total of 60 enrollments is achieved.

For each site, accrual will begin after all applicable approvals are obtained and a Site-Specific Study Activation Notice is issued by the MTN CORE FHI. Once accrual is initiated at each site, study staff will report the number of participants screened for and enrolled in the study to the FHI on a weekly basis throughout the accrual period. Based on this information, FHI will distribute a weekly accrual report to the Protocol Team. In addition, on a monthly basis, the SDMC will report to the Protocol Team the number of participants enrolled based on data received and entered into the study database.

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; 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 all 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 are responsible for developing a standard operating procedure (SOP) for participant accrual and ensuring appropriate recruitment efforts undertaken to meet site-specific accrual goals. The accrual SOP should minimally contain the following elements:

- Site-specific accrual goals
- Methods for tracking accrual goals versus actual accrual
- Recruitment methods and venues
- Methods for identifying the recruitment source of participants 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 Sections 5 and 7 of the protocol and in the visit checklists contained in Section 7 of this SSP Manual. Informed consent procedures are described in SSP Section 5 and instructions for performing clinical and laboratory procedures are in SSP sections 10 and 12, respectively.

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the MTN-007 Protocol Safety Review Team (PSRT) for guidance on the specific action to be taken. PSRT contact details are provided in Section 11 of this manual. Site staff must also complete a protocol deviation form in accordance with the guidelines in Section 16.4 of the MTN Manual of Operations,

http://www.mtnstopshiv.org/sites/default/files/attachments/MTN%20MOP%2016%20for%20copy%20edit%20May%202010_JHH%20CSD.pdf

4.2.1 Definition of Screening

The term "screening" refers to all procedures undertaken to determine whether a potential participant is presumptively eligible to take part in MTN-007. Screening may take place over more than one visit. Participants found to be presumptively eligible will have their final eligibility determination completed at the Enrollment/Baseline Evaluation visit, which must occur within 36 days following the Screening Visit.

4.2.2 Eligibility Determination

All potential participants who meet the inclusion and exclusion criteria and successfully complete all the screening procedures are eligible for enrollment into MTN-007. Final eligibility determination must be completed within 36 days following the Screening Visit.

Documentation to address each of the protocol's inclusion and exclusion criteria must be present in the individual's research record. 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. As a condition of study activation, study sites must establish an SOP that describes how study staff will fulfill this responsibility. This SOP minimally should contain the following elements:

- Eligibility determination procedures for participants, including:
    - During-visit eligibility assessments procedures
    - Post-visit eligibility assessment and confirmation procedures
    - Final confirmation and sign-off procedures prior to enrollment/randomization
    - Documentation
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- QC/QA procedures related to the above (if not specified elsewhere)

Figure 4.1: Timing of Eligibility Assessments for MTN-007

Inclusion and Exclusion Criteria	Assessed At Screening Visit	Assessed At Enrollment Visit
≥ Age of 18 at screening, verified per site SOP	X	
Willing and able to provide written informed consent	X	X
Willing and able to communicate in English	X	X
Must be in general good health	X	X
Willing and able to provide adequate locator information	X	X
Must agree not to participate in other research studies involving drugs, medical devices, or genital products for the duration of study participation	X	X
HIV-1 uninfected at screening according to the standard DAIDS algorithm in Appendix II	X	
Availability to return for all study visits, barring unforeseen circumstances	X	X
A history of consensual RAI at least once in the prior year	X	
Willing to abstain from insertion of anything rectally, including sex toys, other than the study gel for the duration of study participation	X	X
Willing to abstain from RAI for the duration of study participation	X	X
Must agree to use study provided condoms for the duration of the study for vaginal and insertive anal intercourse	X	X
Postmenopausal or using (or willing to use) an acceptable form of contraception (e.g., barrier method, IUD, hormonal contraception, surgical sterilization, or vasectomization of male partner). If the female participant has female partners only, the method of contraception will be noted as a barrier method in the study documentation.	X	X
No abnormalities of the colorectal mucosa, or significant colorectal symptom(s), which in the opinion of the clinician represents a contraindication to biopsy (including but not limited to presence of any unresolved injury, infectious or inflammatory condition of the local mucosa, and presence of symptomatic external hemorrhoids)	X	
No participant reported symptoms and/or clinical or laboratory diagnosis of active rectal or reproductive tract infection requiring treatment per current CDC guidelines or symptomatic urinary tract infection (UTI). Infections requiring treatment include symptomatic bacterial vaginosis, symptomatic vaginal candidiasis, other vaginitis, trichomoniasis, Chlamydia (CT), gonorrhea (GC), syphilis, active HSV lesions, chancroid, pelvic inflammatory disease, genital sores or ulcers, cervicitis, or symptomatic genital warts requiring treatment. Note that an HSV-1 or HSV-2 seropositive diagnosis with no active lesions is allowed, since treatment is not required. Note: In cases of non-anorectal GC/CT identified at screening, one re-screening 2 months after screening visit will be allowed.	X	
No anorectal STI within six months prior to the Screening Visit	X	
Hemoglobin not less than 10.0 g/dL	X	
Platelet count not less than 100,000/mm^3	X	
White blood cell count < 2,000 cells/mm^3 or > 15,000 cells/mm^3	X	
Negative for Hepatitis B surface antigen (HBsAg)	X	

For females: calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula where creatinine clearance in mL/min (140- age in years) x (weight in kg) x (0.85 for female)/72 x (serum creatinine in mg/dL) ***For males:*** calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula where creatinine clearance in mL/min = (140 - age in years) x (weight in kg) x (1 for male)/72 x (serum creatinine in mg/dL)	X	
Serum creatinine > 1.3× the site laboratory upper limit of normal (ULN)	X	
Alanine transaminase (ALT) and/or aspartate aminotransferase (AST) > 2.5× the site laboratory ULN	X	
+1 glucose or +1 protein on urinalysis (UA)	X	
No history of bleeding problems	X	
No history of significant gastrointestinal bleeding in the opinion of the investigator	X	X
No allergy to methylparaben, propylparaben, sorbic acid, and components of N-9	X	X
No known HIV-infected partners	X	X
No history of excessive daily alcohol use (as defined by the CDC as heavy drinking consisting of an average consumption of more than 2 drinks per day for men, and more than 1 drink per day for women), frequent binge drinking or illicit drug use that includes any injection drugs, methamphetamines (crystal meth), heroin, or cocaine including crack cocaine, within the past 12 months	X	X
No anticipated use and/or unwillingness to abstain from the following medications during the period of study participation: a. Heparin, including Lovenox® b. Warfarin c. Plavix® (clopidogrel bisulfate)) d. Rectally administered medications (including over-the-counter products) e. Aspirin f. Non-steroidal anti-inflammatory drugs (NSAIDS) g. Any other drugs that are associated with increased likelihood of bleeding following mucosal biopsy	X	
Per participant report, no use of post-exposure prophylaxis, systemic immunomodulatory medications, rectally administered medications, rectally administered products (including condoms) containing N-9, or any investigational products within the 4 weeks prior to the Enrollment/Baseline Evaluation Visit and throughout study participation	X	
No history of recurrent urticaria	X	X
Any other condition or prior therapy that, in the opinion of the investigator, would preclude informed consent, make study participation unsafe, make the individual unsuitable for the study or unable to comply with the study requirements. Such conditions may include, but are not limited to, current or recent history of severe, progressive, or uncontrolled substance abuse, or renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, or cerebral disease	X	X
For females: a. Pregnant at the Enrollment/Baseline Visit b. Breastfeeding at screening or intend to breastfeed during study participation per participant report	X	X

4.2.3 Definition of Enrollment

Participants will be considered enrolled in MTN-007 when they have been assigned an MTN-007 Clinic Randomization Envelope. The effective point of enrollment is the assignment of the randomized arm (randomization), which occurs at the Enrollment/Baseline Evaluation visit. Further information about randomization can be found in section 4.2.8.

4.2.4 Screening and Enrollment Timeframe

Screening may occur anytime and in multiple visits after the informed consent for screening is signed. Final eligibility determination and Enrollment (Day 0), however, must occur no more than 36 days following provision of informed consent for screening.

Note: If all screening and enrollment procedures are not completed within 36 days of obtaining informed consent for screening due to some unforeseen reason (i.e. family emergency or adverse weather conditions), the participant may repeat the screening process, including the screening informed consent process; however, the PTID will remain the same (see Section 13.3.2 of this manual for further guidance.)

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 visit checklist.

A potential participant who signs or marks the screening informed consent form on August 18, 2010 could be enrolled on any day up to and including September 23, 2010.

Figure 4.2: Sample Enrollment Timeframe Calendar

August 2010						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18 ***Screening ICF Signed***	19	20	21
22	23	24	25	26	27	28
29	30	31				
September 2010						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23 ***Last Day to Enroll***	24	25
26	27	28	29	30		

4.2.5 Screening and Enrollment Logs

The DAIDS SOP for Essential Documents requires study sites to document study screening and enrollment activities on a screening and enrollment log. This log documents the identification of participants who enter pre-trial screening and the chronological enrollment of subjects. A sample log that may be adapted for use at the participating study sites is provided below. The logs must include the following information at a minimum: participant's initials, participant identification (PTID) number, date of screening visits and, if enrolled (randomized), the date enrolled. If the participant is not enrolled the reason must be noted on the log.

Figure 4.3: Sample MTN 007 Screening and Enrollment Log								
Site Name, Clinic Name, and Location:								
	Participant ID	**Is this a Replacement Participant?**	**PTID of Replaced Participant (If not a replacement participant write NA)**	**Date Screened/ Consent Signed***	**Eligible?**	**Enrollment/ Randomization Date**	**If not enrolled, specify reason**	**Staff Initials**
1		Y N			Y N			
2		Y N			Y N			
3		Y N			Y N			
4		Y N			Y N			
5		Y N			Y N			
6		Y N			Y N			
7		Y N			Y N			
8		Y N			Y N			
9		Y N			Y N			
10		Y N			Y N			
11		Y N			Y N			
12		Y N			Y N			
13		Y N			Y N			
14		Y N			Y N			
15		Y N			Y N			
16		Y N			Y N			
17		Y N			Y N			
18		Y N			Y N			
19		Y N			Y N			
20		Y N			Y N			

* Note: Participants should not be considered screened unless they have completed the screening informed consent process.

4.2.6 Assignment of Participant ID Numbers

The MTN Statistical Data Management Center (SDMC), SCHARP, will provide the study site with a listing of Participant Identification (PTID) numbers for use in MTN-007. 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 (the PTID-Name Linkage Log).

Further information regarding the structure of PTIDs for MTN-007 can be found in Section 13 of this manual. PTIDs will be assigned to all potential participants who provide informed consent for screening, regardless of whether they enroll in the study. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts completed. Site staff are responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

Figure 4.4: Sample Site-Specific PTID-Name Linkage Log for MTN-007

	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			

4.2.7 Screening HIV Testing

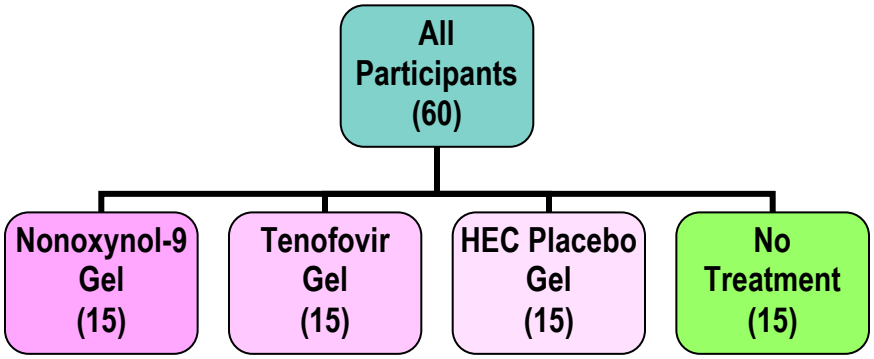
HIV infection status at screening will be assessed using an ELISA test. Blood will be collected and tested per the algorithm in Appendix II of the protocol and instructions are given in the Laboratory Section (section 12) of this SSP.

4.2.8 Random Assignment

4.2.8.1 Overview

At all study sites, participants will be randomly assigned in equal numbers to one of four study arms: Tenofovir 1% gel, 2% Nonoxynol-9 gel, HEC placebo gel and no treatment (no gel). Across sites, approximately 15 people will be assigned to each arm, as noted in Figure 4.5.

Figure 4.5: MTN-007 Participant Randomization Scheme



After the participant's eligibility has been determined and this has been documented in the study source documents, the participant may be randomized to MTN-007. All treatment arm randomizations are double-blinded, meaning that both site staff and participants will not be provided information on the identity of the specific gels to which the participants have been assigned.

The SDMC will generate and maintain the study randomization scheme and associated materials, which consist of the following:

- MTN-007 Clinic Randomization Envelopes (Figures 4-6a, 4-6b, and 4-6c)
- MTN-007 Clinic Randomization Envelope Tracking Records (Figure 4-7)
- MTN-007 Prescriptions (Figure 4-8)
- MTN-007 Replacement Participant Prescriptions (Figure 4-9)
- MTN-007 Pharmacy Randomization Envelopes
- MTN-007 Pharmacy Randomization Envelope Tracking Records
- MTN-007 Participant-specific Pharmacy Dispensing Records
- MTN-007 Replacement Participant Pharmacy Dispensing Records

MTN-007 Clinic Randomization Envelopes: MTN-007 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-007 Clinic Randomization Envelope is assigned to a participant, it may not be re-assigned to any other participant. All envelopes are sealed with blue security tape that, when opened, reveals the word "OPENED" in the residue of the tape.

MTN-007 Clinic Randomization Envelope assignment to eligible participants will be documented on the MTN-007 Clinic Randomization Envelope Tracking Record that will accompany the Clinic Randomization Envelope shipment to each site. The act of assigning an MTN-007 Clinic Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once an MTN-007 Clinic Randomization Envelope is assigned, the participant is considered enrolled in the study.

Each MTN-007 Clinic Randomization Envelope will contain an MTN-007 prescription that will be pre-printed with the assignment of "Gel" or "No Treatment (No Gel)". For "Gel" participants, there will be two prescriptions in the Clinic Randomization Envelope: one MTN-007 prescription will be for the dispensing of a single prefilled gel applicator for the single dose administration (titled "Single Dose Gel") that occurs at the Treatment 1 Visit; the second prescription (titled "Seven-Day Gel") will be for eight (8) prefilled applicators of gel given to the participant at the Treatment 2 Visit. This will provide study product for seven (7) consecutive days and one extra applicator for use if needed. For "No Treatment (No gel)" participants, there will be one "No Treatment (No Gel)" prescription in the Clinic Randomization Envelope as well as a blank piece of paper.
All MTN-007 prescriptions will be produced as a two-part no carbon required (NCR) form pre-printed with the CRS name, CRS location, DAIDS site ID, and MTN-007 Clinic Randomization Envelope number. After opening the Clinic Randomization Envelope, prescriptions for gel participants will be stored (along with the opened envelope) in the participant's study notebook until the Treatment 1 visit. For no treatment participants, the prescription will be completed on the day of randomization and clinic staff will then separate the two parts of the prescription and deliver or fax the white original (white) copy to the pharmacy. The yellow copy of the no treatment prescription will be retained in the participant's study notebook.

For gel participants, the single dose gel prescription will be completed and provided to the pharmacy at the Treatment 1 Visit, and the seven-dose gel prescription will be used at the Treatment 2 visit. Each site will develop an SOP for writing study prescriptions and dispensing study gel to participants.

The SDMC will also provide site clinic staff with blank "replacement" prescriptions, meaning the prescriptions will not contain an assignment to either gel or no gel. These blank MTN-007 prescriptions will be used for replacement participants only.

MTN-007 Pharmacy Randomization Envelopes: MTN-007 Pharmacy Randomization Envelopes will be shipped from the MTN SDMC directly to each study pharmacy. These envelopes are prepared in a similar fashion to the Clinic Randomization Envelopes and are linked to the Clinic Randomization Envelopes by envelope number. MTN-007 Participant-specific Pharmacy Dispensing Records are contained in the pharmacy randomization envelopes, and will be used by pharmacy staff to document dispensation of study gel applicators to the participant. These records will be pre-printed with the site CRS name, MTN-007 Pharmacy Randomization Envelope number, and information indicating (blinded) gel assignment This Participant-specific Dispensing Record will also contain a place to record the PTID and a space to adhere the tear-off labels of dispensed applicators of study gel. 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.

The SMDC will also provide site pharmacy staff with blank "replacement" MTN-007 Participant-specific Pharmacy Dispensing Records, meaning the records will not contain any pre-printed information. These blank MTN-007 Participant-specific Pharmacy Dispensing Records will be used for replacement participants only.

Figure 4-6a
Sample MTN-007 Clinic Randomization Envelope

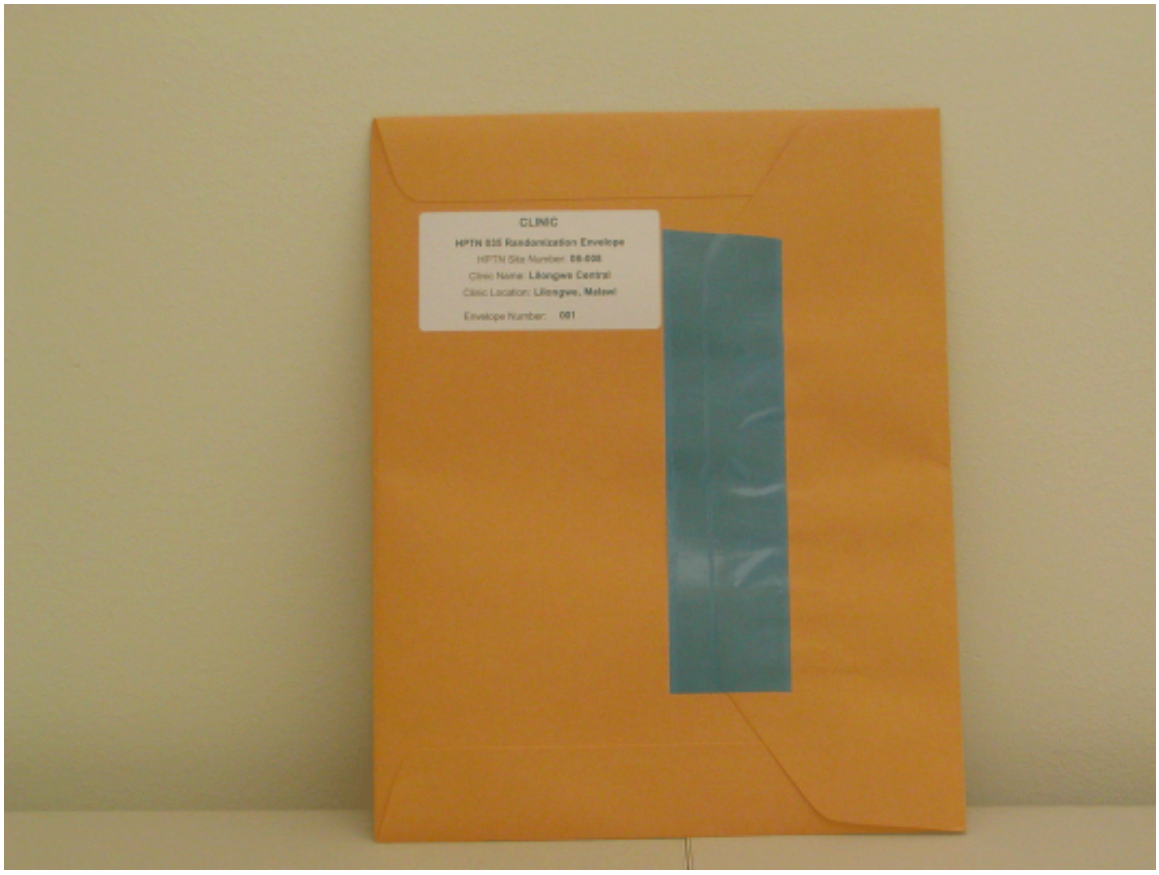


Figure 4-6b
Sample MTN-007 Clinic Randomization Envelope — Close-Up View of Label

CLINIC

MTN-007 Randomization Envelope

DAIDS CRS ID: **30309**

CRS Name: **Alabama Microbicide CRS**

CRS Location: **Birmingham, AL**

Envelope Number: **999**

Figure 4-6c
Sample Opened MTN-007 Clinic Randomization Envelope

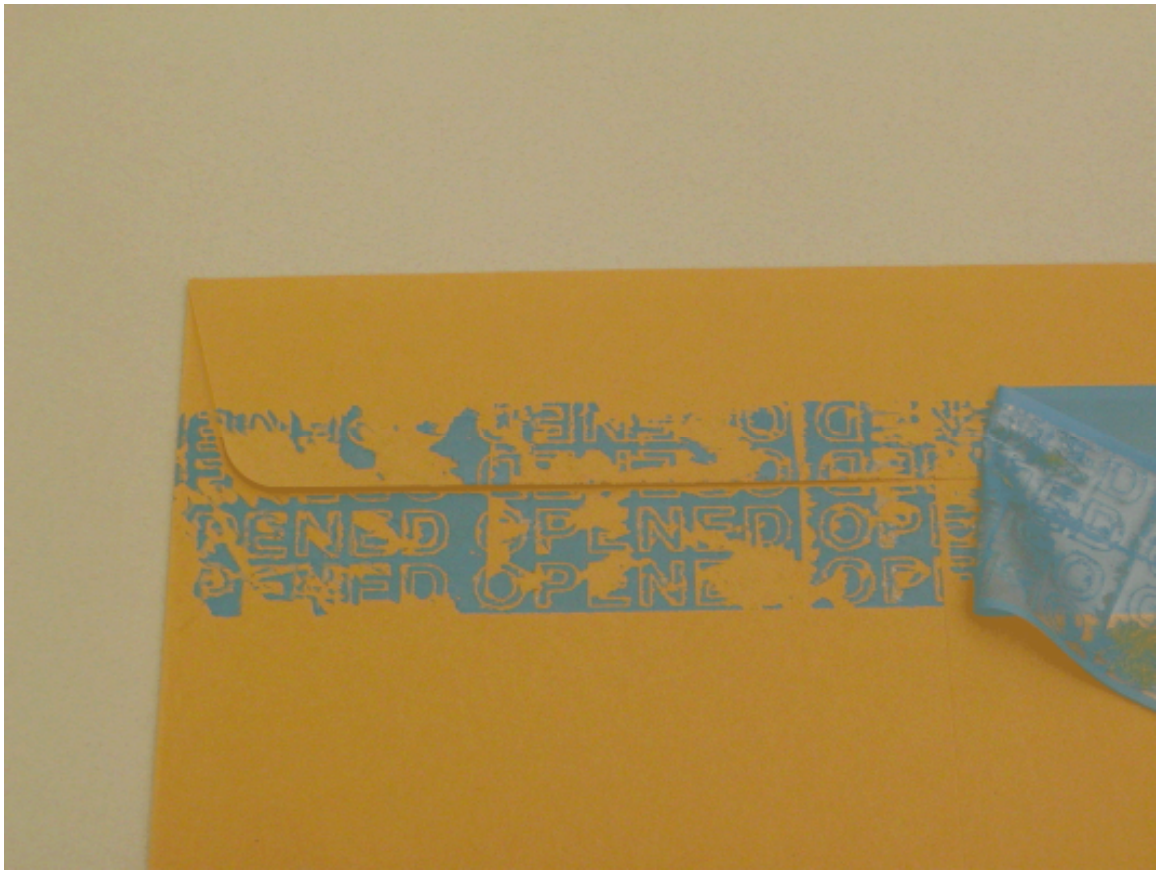


Figure 4-7
Sample MTN-007 Clinic Randomization Envelope Tracking Record

MTN 007 Clinic Randomization Envelope Tracking Record

Page 1

CRS Name:	**Alabama Microbicide CRS**	**DAIDS Site ID:**	**30309**
CRS Location:	**Birmingham, AL**		

Instructions: Complete one row each time a clinic randomization envelope is assigned to an MTN 003 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 (hh:mm) (24-hour clock)	Clinic Staff Initials
0001				
0002				
0003				
0004				
0005				

Figure 4-8
Sample MTN-007 Prescription

MTN-007 PRESCRIPTION – SINGLE DOSE GEL

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.

CRS Name:	**Pre-print**	**DAIDS Site ID:**	**Pre-print**
CRS Location:	**Pre-print**	**Clinic Randomization Envelope #:**	**Pre-print**

Participant ID: ☐☐☐-☐☐☐☐☐-☐

Did the participant provide written informed consent for enrollment into MTN-007? ..... Yes ☐ No ☐ Clinic Staff Initials _____

Assignment: Gel

MTN-007 Study Gel (Tenofovir 1% gel, 2% Nonoxynol-9 gel, or HEC placebo gel)

Sig: Insert entire contents of one (1) applicator rectally. This single rectally administered dose will be observed by the site clinician.

Quantity: **One (1) pre-filled applicator of study gel.**

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: ☐☐-☐☐☐-☐☐
dd *MMM* *yy*

Clinic Staff Instructions: Once form is complete, deliver original white copy (Pharmacy) to pharmacy; retain yellow copy (Clinic) in participant study notebook.

Pharmacy: Dispense one (1) pre-filled applicator of study gel.

Clinic Staff Initials: _____ Date: ☐☐-☐☐☐-☐☐
dd *MMM* *yy*

Pharmacy

Figure 4-9
Sample MTN-007 Replacement Prescription

MTN-007 REPLACEMENT PRESCRIPTION – GEL

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.

CRS Name:	Pre-print	DAIDS Site ID:	Pre-print
CRS Location:	Pre-print		

Participant ID: ☐☐☐-☐☐☐☐☐-☐

Did the participant provide written informed consent for enrollment into MTN-007? ..... Yes ☐ No ☐ Clinic Staff Initials _____

Clinic Staff Instructions: To complete the items below, obtain the MTN-007 prescription assigned to the ***participant being replaced***. Complete the information below based on the randomization information contained on that prescription.

Participant ID of participant being replaced: ☐☐☐-☐☐☐☐☐-☐

Clinic Randomization Envelope # of participant being replaced: ☐☐☐

MTN-007 Study Gel (Tenofovir 1% gel, 2% Nonoxynol-9 gel, or HEC placebo gel)

Authorized Prescriber: Mark one of the boxes below to indicate single-dose or 8 dose dispensation.

☐ Sig: Insert entire contents of one (1) applicator rectally. This single rectally administered dose will be observed by the site clinician.
Quantity: **One (1) pre-filled applicator of study gel.**

OR

☐ Sig: Insert entire contents of one (1) applicator rectally once each day before bedtime for seven consecutive days.
Quantity: **Eight (8) pre-filled applicators of study gel.**

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: ☐☐-☐☐☐-☐☐
dd *MMM* *yy*

Clinic Staff Instructions: Once form is complete, deliver original white copy (Pharmacy) to pharmacy; retain yellow copy (Clinic) in participant study notebook.

Clinic Staff Initials: _____ Date: ☐☐-☐☐☐-☐☐
dd *MMM* *yy*

Pharmacy

4.2.8.2 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 his/her signing the informed consent form. Random assignment will also take place after the participant has:

- Completed the informed consent process for Storage and Future Testing of Specimens
- Completed the CASI Baseline Behavioral Questionnaire (BBQ)
- Provided blood for plasma archive

4.2.8.2.1 In-Clinic Randomization Procedures

The in-clinic randomization procedures listed below (Steps C1-C6) then will be performed.

C1. Obtain the next sequential Clinic Randomization Envelope and inspect it to verify that the correct envelope has been obtained and there is no evidence that the envelope has been tampered with or previously opened. Assign the envelope to the participant and document assignment on the MTN-007 Clinic Randomization Envelope Tracking Record by recording the PTID, date assigned, time assigned, and clinic staff initials in the row corresponding to the assigned envelope number.

C2. Open the assigned Clinic Randomization Envelope; alternatively, allow the participant to open it. Remove the prescription(s) from the envelope and verify that the envelope number printed on the prescription(s) corresponds to the envelope number printed on the Clinic Randomization Envelope label. If the envelope does not contain a prescription, or if any information pre-printed on the prescription appears to be incorrect, contact the MTN SDMC Project Manager and the FHI Clinical Research Manager. Do not proceed with randomization of this or any other participant until instructed to do so by the MTN SDMC.

C3. Inform the participant of his/her assignment — to either gel or no treatment (no gel)— and provide appropriate information, instructions, and counseling applicable to the assignment.

C4. For no treatment (no gel) participants: complete the prescription as follows:

In the top section of the prescription, record the PTID assigned to the participant in the boxes provided and mark whether the participant provided informed consent to take part in the study. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her initials beside the box.

The middle section of the prescription is completed by pharmacy staff.

The bottom section of the prescription may be completed by any clinic staff member. If this section is completed by a clinic staff member other than the person who opened the Clinic Randomization Envelope, the clinic staff member who completes this section must have access to source documentation of the date upon which the Clinic Randomization Envelope was opened.

C5. For gel participants: complete the single dose gel prescription at the Treatment 1 visit as follows:

In the top section of the prescription, record the PTID assigned to the participant in the boxes provided and mark whether the participant provided informed consent to take part in the study. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her initials beside the box.

The middle section of the prescription must be completed by a study staff member designated in the site's delegation of duties as an authorized prescriber of study product. This person must be listed as an investigator (either IoR 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.

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 product to be dispensed to study participants. This person may be the authorized prescriber who completes the middle section of the prescription or may be another clinic staff member. If this section is completed by a clinic staff member other than the person who opened the Clinic Randomization Envelope, the clinic staff member who completes this section must have access to source documentation of the date upon which the Clinic Randomization Envelope was opened.

These same procedures are followed at the Treatment 2 visit for gel participants, at which time the seven-day gel prescription is completed.

C6. Double-check the accuracy of all entries and then separate the two sheets of the completed prescription. Retain the yellow copy in the participant study notebook in the clinic. Also retain the Clinic Randomization Envelope in the participant study notebook. Clinic Randomization Envelopes may be hole-punched after they have been opened and their contents have been removed.

C7. Deliver the white original prescription to the study pharmacy. This may be done by the participant or by a study staff member.

4.2.8.2.2 In-Pharmacy Randomization Procedures

Corresponding to steps C1-C7 above, in-pharmacy randomization procedures are specified in the *MTN-007 Pharmacist Study Product Management Procedures Manual*. If pharmacy staff identify possible errors on the original prescription, they will return the prescription to clinic staff for clarification or correction. If corrections are required, corrections must be made on both the white original prescription and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete original prescriptions.

4.2.8.3 Replacement Participants

The purpose of replacing participants is to preserve the power of the study in the cases of product discontinuation or non-adherence. Additional participants may be enrolled at the discretion of the protocol team to replace participants who have been permanently discontinued from study product as well as participants who are non-adherent to study product.

Once the protocol team has determined a particular participant requires replacing, the SDMC will provide the affected site with information on when the replacement participant should be enrolled. The SDMC will also provide the site with the PTID of the participant being replaced.

Site clinic staff will *not* assign a clinic randomization envelope to replacement participants. Rather, site clinic staff will complete the applicable MTN-007 Replacement prescription(s) for each replacement participant by transcribing the randomization information from the MTN-007 prescription(s) assigned the participant being replaced onto the Replacement prescription. For replacement participants, the act of completing the MTN-007 Replacement prescription is the effective act of randomization and enrollment in the study. Once the applicable MTN-007 Replacement prescription is completed, the replacement participant is considered enrolled in the study.

4.3.8.3.1 Specific Procedures for Replacement Participants

For each replacement participant, treatment assignment (gel or no treatment) will take place after the participant has been confirmed as eligible and willing to take part in the study, as documented by his/her signing the informed consent form. Treatment assignment will also take place after the replacement participant has:

- Completed the informed consent process for Storage and Future Testing of Specimens
- Completed the CASI Baseline Behavioral Questionnaire (BBQ)
- Provided blood for plasma archive

In-Clinic Randomization Procedures for Replacement Participants
The in-clinic procedures listed below (Steps C1-C6) then will be performed.

C1. Obtain the study notebook of the participant being replaced. Obtain the completed prescription(s) of the participant being replaced.

C2. Inform the replacement participant of his/her assignment — to either gel or no treatment (no gel) — as indicated by the completed prescription(s) of the participant being replaced.

C3. For replacement participants assigned to no treatment (no gel) participants: obtain a blank "MTN-007 REPLACEMENT PRESCRIPTION – NO TREATMENT (NO GEL)" prescription and complete the prescription as follows:

In the top section of the prescription, record the PTID assigned to the participant in the boxes provided and mark whether the participant provided informed consent to take part in the study. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her initials beside the box.

The middle section of the prescription labeled "Clinic Staff Instructions" is completed by clinic staff. In this section, record the PTID of the participant being replaced as well as the Clinic Randomization Envelope number of the participant being replaced.

The bottom section of the prescription may be completed by any clinic staff member.

C4. For replacement participants assigned to gel, obtain a blank "MTN-007 REPLACEMENT PRESCRIPTION – GEL" prescription and complete the prescription at the Treatment 1 visit as follows:

In the top section of the prescription, record the PTID assigned to the participant in the boxes provided and mark whether the participant provided informed consent to take part in the study. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her initials beside the box.

The middle section of the prescription labeled "Clinic Staff Instructions" is completed by clinic staff. In this section, record the PTID of the participant being replaced as well as the Clinic Randomization Envelope number of the participant being replaced.

The middle section of the prescription labeled "MTN-007 Study Gel….." may be completed by any clinic staff member authorized in the site's delegation of duties to determine the quantity of product to be dispensed to study participants. This person may be the authorized prescriber, or may be another clinic staff member. The authorized prescriber name, signature, and date portions must be completed by a study staff member designated in the site's delegation of duties as an authorized prescriber of study product. This person must be listed as an investigator (either IoR or sub-investigator) on the current FDA Form 1572. At the Treatment 1 Visit, the box for one (1) pre-filled applicator should be marked. The date recorded in this section of the prescription is the date upon which the authorized prescriber signs the prescription.
These same procedures are followed at the Treatment 2 visit for replacement participants assigned to gel, at which time a (new) blank "MTN-007 REPLACEMENT PRESCRIPTION – GEL" prescription is obtained and completed, indicating eight (8) pre-filled applicators are prescribed.

C5. Double-check the accuracy of all entries and then separate the two sheets of the completed prescription. Retain the yellow copy in the participant study notebook in the clinic.

C6. Deliver the white original prescription to the study pharmacy. This may be done by the participant or by a study staff member.

In-Pharmacy Randomization Procedures for Replacement Participants

Corresponding to steps C1-C6 above, in-pharmacy randomization procedures for replacement participants are specified in the *MTN-007 Pharmacist Study Product Management Procedures Manual.* If pharmacy staff identify possible errors on the original replacement prescription, they will return the replacement prescription to clinic staff for clarification or correction. If corrections are required, corrections must be made on both the white original prescription and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete original prescriptions.

Section 5. Informed Consent

This section provides information on informed consent procedures for MTN-007. MTN-007 involves three types of informed consent:

- Informed consent for screening
- Informed consent for enrollment
- Informed consent for long term specimen storage and possible future research testing

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 random assignment, use of study products and completion of follow-up visits and procedures. For enrolled participants, informed consent for long term specimen storage and possible future research is optional. Participants may choose not to consent to long term specimen storage and possible future research testing and still be enrolled in the study. Consenting to long term storage is to be completed at the enrollment visit and at the completion of the enrollment consent process.

5.1 Overview of Informed Consent for Screening and Enrollment

Written informed consent must be obtained for all MTN participants prior to the performance of any protocol-specified screening or enrollment procedures and assessments. (See overview in Section Appendix 5-1)

Informed consent is a process by which an individual voluntarily expresses the willingness to participate in research, after having been informed of all aspects of the research that are relevant to the participant's 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 with four key considerations, each of which is described below. See Section 4.8 of the ICH GCP guideline and the informed consent section of the DAIDS SOP for Source Documentation for detailed guidance on the informed consent process and documentation requirements.

US regulations 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 his/her staff to deliver complete and accurate information to potential research participants.

However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It also is 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

5.1.1 Deliver Required Information in an Understandable Manner

As a starting point at the screening visit, assess participant literacy. If the participant is literate, give him/her a copy of the informed consent form to read. Also provide the participant with other IRB approved informational materials developed to complement the informed consent form. If the participant is not literate, read the materials to him/her verbatim. Because many of the research concepts and terms many be unfamiliar, even to literate people, the consent form must be reviewed very carefully with each potential volunteer. It is suggested that each paragraph be read by the study staff member conducting the consent discussion and that the key points be emphasized, pausing after each paragraph to allow for questions and to probe for understanding. A checklist highlighting key points may serve as a useful guide for reviewing the consent with the potential volunteer. For example, you may note the main points described in each paragraph of the informed consent form and ask if the participant has questions or concerns about each point. Listen carefully to the questions and/or concerns expressed by the participant and discuss them thoroughly. Take as much time as needed to address each question and concern.

Remember: If the participant is not literate, an impartial witness must be present during the entire informed consent discussion. The witness will be asked to sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant and that informed consent was freely given by the participant. The ICH GCP guideline identifies an "impartial" witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. The CORE has received guidance from the US Food and Drug Administration's GCP office stating that the witness need not be "totally unaffiliated with the study. It may be possible, for example, to designate a 'subject advocate' who would be available at each site." Each site must specify its procedures for obtaining informed consent from illiterate persons in its SOP for obtaining informed consent. The SOP should define who may serve as the witness to the informed consent process. It is recommended that each site seek IRB review and approval of these procedures.

5.1.2 Obtain Consent in a Setting Free of Coercion

During the informed consent discussion, take care not to overstate the possible benefits of the study, nor to understate the risks. Also emphasize to the participant that the availability of medical care and other services routinely obtained form the recruitment site and/or research institution will not be affected by the volunteer's decision whether or not to take part in the study. Encourage the participant to take as much time as he/she needs and to talk about his/her potential participation with others, if he/she chooses, before making a decision.

NOTE: If the participant is not literate, and therefore a witness is present during the entire informed consent discussion, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the participant, with emphasis on the fact that the witness is there as a protection for the participant, not as an agent for the study.

5.1.3 Confirm Participant Comprehension

The participant must not be asked to agree to take part in the screening/study or to sign or make his/her mark on the informed consent form until he/she fully understands the screening process/study.

Study staff are responsible for implementing procedures to ensure that each participant understands the screening process and the study prior to signing/marking the informed consent forms and undertaking any screening or study procedures. Study staff should emphasize with potential volunteers aspects of the study that may be most challenging for them. It is critical that volunteers fully understand what the screening procedures are or participation in the study entails before agreeing to participate.

One suggested approach to assessing comprehension is to use a "quiz" (either oral or written) or other assessment tool which participants must complete prior to signing/marking the informed consent form. A sample assessment is included at the end of this section. Another approach is to use open-ended questions to ascertain participant understanding during the informed consent discussion. For sites that choose to adopt tools such as those included at the end of this section, detailed use instructions must be specified in the site SOP for obtaining informed consent.

Regardless of the method used to assess comprehension, if the assessment results indicate misunderstanding of certain aspects of the study, review those aspects again until the participant fully understands them. If after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the study, do not ask him/her to sign/mark the informed consent form or continue screening for the study. Similarly, if the participant has concerns about possible adverse impacts on him/her or indicates that he/she may have difficulty adhering to the study requirements, do not ask him/her to sign the informed consent form. If the participant has serious concerns about family members or others learning that he/she is in the study and the participant is not willing to discuss this with them in advance, the volunteer should not be asked to sign the consent.

5.1.4 Document the Process

US regulations require that informed consent be documented by "the use of a written informed consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

It is essential that the date documented on the consent form either precedes or coincides with the (first) study screening date. In addition, enter a note in the participant chart documenting that informed consent was obtained prior to the initiation of any study procedures (Section Appendix 5-2 gives an example of an informed consent coversheet). Finally, regulations require that participants be given a signed copy of the informed consent form. If a participant opts not to receive a copy, document this in a chart note.

Signatures on the consent forms must be the legal name of the participant and not include fabricated or falsified names or nicknames. Sites are not required to verify a person's legal name; however, if the site becomes aware that a person had not used his/her legal name, then the instructions provided for this situation in the DAIDS SOP for Source Documentation must be followed.

Initials cannot be used for the family name (last name). Use of initials for first names is discouraged, but not prohibited as long as it is acceptable per the policy of the local institution. The consent must be dated by the person signing the form; it is not acceptable for study staff to complete the date for another signer. All entries must be in ink.

NOTE: If the participant is not literate, the witness who was present during the informed consent discussion must sign and date the informed consent form to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by the participant, and that informed consent was freely given by the participant. If the participant cannot write her name or the date, this should be documented in the research record, in a chart note and/or on a face sheet or other documentation tool. In addition, the participant printed name, signature and signature date blocks on the informed consent form should be completed as follows:

- The "participant's printed name" block should be left blank and the name should be recorded below the line by the person conducting the consent discussion, and initialed and dated. The participant chart should include documentation that the participant could not sign for himself/herself (e.g., documentation on the informed consent coversheet).
- The participant should make his/her mark in the "participant's signature" block.
- The "participant signature date" block should be left blank and the date should be recorded below the line by the person conducting the consent discussion, and initialed and dated.

Section appendices 5-3 and 5-4 give an overview and example of this process.

5.2 Informed Consent for Specimen Storage

Storage of specimens remaining after trial completion is optional for each site. If a site chooses to store leftover biological specimens after all of the protocol-specified assessments and quality control procedures are completed, separate written informed consent must be obtained from each participant. This consent may be obtained at the Enrollment visit. Participants may choose not to have their specimens stored for possible future research testing and still enroll/remain in the study. To facilitate completion of CRFs at the end of the study and management of specimens, sites should keep a record that can be used to ascertain and verify who signed the consent for storage and future testing of specimens. For participants who do not consent to specimen storage and possible future research testing, specimens collected and stored on-site per protocol will be retained until the study is completed and all protocol-specified testing has been completed. Thereafter, any remaining specimens collected from these participants will be destroyed.

5.3 Informed Consent SOP

The DAIDS SOP for Source Documentation provides detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS SOP must be met. In order to also meet some of the suggestions listed in the DAIDS SOP, site staff may consider the use of an informed consent "coversheet" similar to the example included in Section Appendix 5-2.

The above describes aspects of obtaining informed consent from study participants prior to initiating their involvement in the study. Given the ongoing nature of informed consent, key elements of informed consent also should be reviewed at all study follow-up visits. At these visits, study staff should review key elements of informed consent with the participant, focusing on the remainder of their study participation.

As a condition of study activation, each study site must establish an SOP for obtaining informed consent from potential study participants. This SOP should reflect all of the information provided in this section and minimally should contain the following elements:

- 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, including specifications of who may serve as a witness to the informed consent process
- Storage locations for blank informed consent forms
- Storage location of completed informed consent forms
- Procedures (e.g., color-coding) to ensure that the three study informed consent forms are easily distinguished and used appropriately
- Procedures for implementing a change in the version of the informed consent form
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- QA/QC procedures related to the above (if not specified elsewhere)
- Attached copies and instructions for use of all forms, worksheets, checklists, etc., to be used during the informed consent process

5.4 Storage of Consent Forms

All consent forms completed during the screening and enrollment process must be retained even if the participant was not enrolled in the study. It is acceptable for sites to maintain consents in a file separate from a subject's research record and to separate those for enrolled participants from those screened but not enrolled, provided that the sites do this consistently for all subjects. Sites should maintain any subsequent versions of the consent in the same manner.

5.5 Informed Consent Support Materials

Site-specific informed consent forms: The informed consent forms used at all sites must be reviewed and approved by study site IRBs and DAIDS 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 all sites consider the use of color-coding or other techniques to ensure that the various 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. Care must be taken to use the correct forms for long term specimen storage and possible future research testing.

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 gel applicator
- Rectal Insertion Diagram/Pictures (see Section 9 of this SSP)
- Sample randomization envelopes
- Other randomization explanation visual aids (e.g., sack or box containing four items of different colors)

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 him/her. The sample MTN-007 Enrollment Informed Consent Comprehension Checklist (see Section Appendix 5-5) 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. Sites may choose to adapt the checklist; however all checklists require approval from the MTN CORE (FHI) prior to use.

The comprehension checklist will be administered to each potential participant after they have completed the informed consent discussions described above and before asked to sign or mark 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, however this is not a requirement per se. 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 most recently spoke with him/her or 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 them 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 the sample checklist (Question 1) is "study is testing four gels." If the potential participant does not mention this in his/her initial response to Question 1, the study staff member may then ask "Can you tell me how many products are 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 may explain the correct information before proceeding to another question, or defer explanation of the correct information until after the entire checklist has been administered.

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 his/her response to a previous question. However, if staff is confident that a previous response was adequate, the specific question and/or point do not need to be repeated.

It is expected that study staff administering the informed consent process and checklist will be sufficiently knowledgeable about MTN-007 to make good judgments about potential participants' understanding of the required information. It is possible that a participant might repeat the correct information, yet the staff member may not be convinced that they really understand 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 or marking of 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.

Section Appendix 5-1
Overview of MTN-007 Enrollment Informed Consent Process

Briefly **describe the steps** in the enrollment consent process and tell the participant how long it takes to complete. ASK Do they have time to complete this today?	• If yes, proceed. • If no, schedule return appointment.
ASK Are they ready to have the **informed consent form** read to them or read it him/herself?	• If yes, proceed. • If not, determine what is needed and provide information or schedule return appointment.
Read consent form, section by section, asking if the participant has questions and discussing as you go along. ASK Do they feel comfortable that they understands all aspects of the study?	• If yes, proceed. • If not, determine what is needed and provide more information at that time or schedule return appointment.
Administer **comprehension checklist.** ASK All questions/topics on the checklist. **REQUIRES 100% COMPREHENSION**	• If participant demonstrates comprehension of all required topics, proceed. • If not, discuss misunderstandings and probe problem areas with open-ended questions. Provide information and any other materials as needed to resolve misunderstandings. Continue discussing until comprehension of all required topics is demonstrated. • If participant is fatigued or requests more time, or if staff judge that participant needs more time, schedule return appointment and repeat steps in the process as needed.
Complete all name, signature, and date blocks on the enrollment informed consent form. Offer participant a copy of the form. Document the process per site and DAIDS SOPs.	• Proceed with enrollment procedures (per protocol and this manual).

Section Appendix 5-2
Sample Informed Consent Coversheet for MTN-007

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?	☐ Yes ☐ No ⇒ STOP. Participant is not eligible for MTN-007.
Date of informed consent process/discussion:	
Start time of informed consent process/discussion:	
Language of informed consent process/discussion:	English
Was the informed consent process/discussion conducted according to site SOPs for MTN-007?	☐ Yes ☐ No ⇒ Record and explain departures from site SOPs below.
Can the participant read?	☐ Yes ☐ 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?	☐ Yes ☐ No ⇒ Explain below.
Were all participant questions answered?	☐ Yes ☐ No ⇒ Explain below.
Did the participant comprehend all information required to make an informed decision?	☐ Yes ☐ No ⇒ Explain below.
Was the participant given adequate time/opportunity to consider all options before making his/her informed decision?	☐ Yes ☐ No ⇒ Explain below.
Did the participant accept a copy of the informed consent form?	☐ NA (participant chose not to provide informed consent) ☐ Yes ☐ No ⇒ Offer alternative form of study contact information to participant.
End time of informed consent process/discussion:	
Notes/Comments (continue on back if needed):	
Signature of study staff person completing informed consent process/discussion (and this coversheet):	

Section Appendix 5-3
Summary of Considerations for Obtaining Informed Consent from Illiterate Persons

- Each site must specify procedures for obtaining and documenting informed consent from illiterate persons in its SOP for obtaining informed consent. These procedures must be consistent with the DAIDS SOP for Source Documentation and must be followed each time informed consent is obtained. It is recommended that each site seek IRB/EC review and approval of these procedures.

- An impartial witness must be present during the entire informed consent discussion with an illiterate participant. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant.

- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.

- Take care to minimize the perception of coercion due to the presence of the witness.

- The study staff member who completes the informed consent process/discussion with the participant should enter the participant's name below the "participant's printed name" block on the consent form, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.

- The participant should make her mark in the "participant's signature" block.

- The study staff member who completes the informed consent process/discussion with the participant should enter the date upon which the participant made her mark on the informed consent form below the "participant signature date" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.

- Refer to Section 4.8 of the ICH GCP guideline and the informed consent section of the DAIDS SOP for Source Documentation for additional information.

Section Appendix 5-4
Example of Completion of Informed Consent Form Signature Lines for Illiterate Participants

SIGNATURES

Participant Name	Participant Signature/Mark	Date
(print) **Jane Doe**		**25 July 2009**

Participant name and date written by Suzy Coordinator. SC 25JUL 09

Suzy Coordinator		**25 July 2009**
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date

Mary Witness		**25 July 2009**
Witness Name (print)	Witness Signature	Date

Section Appendix 5-5
MTN-007 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 men and women like using the gel rectally		
		Testing to learn if the gel products are safe		
2	What do you understand that you are being asked to do in this study?	Use condoms and rectally applied study gel as required		
		Have rectal exams		
		Not get pregnant in the next 21 weeks		
		Come for follow-up visits		
3	What do you understand are possible risks to being in this study?	Possibility of social harms		
		Gel may have side effects		
		Gel may irritate skin inside or outside rectum		
4	What will happen if you do not join the study?	No effect on access to care		
		Free to make own decision about joining		
5	Please tell me about the different groups in the study.	There will be 3 different gels tested in the study (3 gel groups) and 1 no gel group; 4 groups total		
6	How will the information about you be protected?	Participant information kept under lock and key		
		Only people working on study have access to my information		
7	What are the benefits to participating in the study?	HIV/STD Counseling, HIV/STI Risk Reduction Counseling, tests, clinical care, benefit to science or community		
8	What should you do if you have any questions about the study?	Must articulate how to contact staff		

Outcome:

☐ Demonstrated comprehension of all required points, decided to enroll in study.

☐ Demonstrated comprehension of all required points, decided not to enroll in study.

☐ Demonstrated comprehension of all required points, deferred enrollment decision

☐ Did not demonstrate comprehension of all required points (yet), needs more time/discussion.

☐ Unable to demonstrate comprehension of all required points, consent process discontinued.

☐ Other (specify):_____

Staff Signature:

Optional Comment Categories:

a. Answered correctly on first try

b. Could not answer at first, but answered correctly after probing

c. Answered incorrectly at first, but answered correctly after discussion

d. Not able to answer correctly at this time

e. Other (describe)

Section 6. Participant Follow-up

This section provides information on requirements and procedures for participant follow-up.

6.1 Study Follow-up Plan

The target accrual of participants is expected to be completed within five months from the time of the first site activation. The protocol team will actively monitor and manage the accrual process to ensure that the enrollment occurs within the specified time frame. Each enrolled participant will be followed through the Follow-up Phone Assessment/Termination Visit, which may occur from Day 28 to Day 77.

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.

6.2 Types of Follow-up Visits

Scheduled Visits are those visits required per protocol. The protocol specifies that, after Screening and Enrollment visits, follow-up visits occur at Treatment 1, Follow-up Phone Assessment, Treatment 2, Final Clinic Visit, and Follow-up Phone Assessment/Termination Visit. All scheduled follow-up visits are pre-assigned a visit code for purposes of data management as described in Section 13 of this manual.

Interim Visits are those visits that take place between scheduled visits. More specifically, a visit is considered an interim visit when a participant presents for additional procedures or assessments beyond the required procedures for a scheduled visit. There are a number of reasons why interim visits may take place (see protocol Section 7.8). Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 13 of this manual.

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 five follow up visits: three in-clinic visits and two follow-up phone calls during the course of the study. For MTN-007, randomization is the effective point of enrollment and enrollment is considered Day 0. Targeted visits dates are based on the day the previous visit was completed. Please refer to the data collection section of this SSP (Section 13) for further details.

The MTN Statistical and Data Management Center (SDMC) will provide each site with a visit scheduling tool that can be used to generate follow-up visit schedules for enrolled participants.

6.3.2 Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the protocol allows for visits to be completed within a visit window. For each required study visit, there is a visit window specifying which study days the visit is allowed to be completed. The study visit windows for MTN-007 are outlined in Section 13 of this manual.

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at specific intervals and every effort should be made to do so. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the visit schedule.

6.3.3 Visits Conducted Over Multiple Days: "Split Visits"

All procedures specified by the protocol to be performed at a particular follow-up visit ideally 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, if the participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the visit window. See Section 13 for relevant visit coding and data collection instructions.

6.3.4 Missed Visits

For participants who do not complete any part of a scheduled visit within the visit window, the visit will be considered "missed" and a Missed Visit case report form will be completed to document the missed visit. Section 13 gives detailed information regarding the completion of the Missed Visit form.

6.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Sections 7.2 through 7.7. Highlighted for reference below are the primary procedural requirements required at each in-person clinic visit (Enrollment/Baseline Evaluation, Treatment 1 Visit, Treatment 2 Visit, and Final Clinic Visit):

- Review/update locator information
- Review/update medical history
- Review/update menstrual history (females only)
- Review/update concomitant medications
- HIV/STI Risk Reduction Counseling
- Urine Pregnancy Test (females of childbearing age only)
- Distribute condoms
- Provide reimbursement for study visit

Additionally, there are further procedures that are completed at certain visits, as follows:

- Document pre-existing conditions (Enrollment)
- HIV pre- and post-test counseling (Final Clinic Visit; only if indicated at Enrollment)
- Protocol Adherence Counseling (Enrollment, Treatment 1 and Treatment 2)
- Product Use Counseling (Enrollment, Treatment 1, and Treatment 2)
- Contraceptive Counseling (Enrollment, Treatment 1 and Treatment 2)
- Baseline Behavioral Questionnaire – CASI (Enrollment)
- Phone reporting system (between Treatment 2 and Final Clinic Visit)
- Product Acceptability Questionnaire – CASI (Final Clinic Visit)
- Physical Exam (Enrollment, Treatment 1, and Final Clinic Visit; only if indicated at Treatment 2)
- Rectal Exam (Enrollment, Treatment 1, and Final Clinic Visit; only if indicated at Treatment 2)
- AE Assessment (Treatment 1, Treatment 2, and Final Clinic Visit)
- Dipstick urinalysis (Final Clinic Visit)
- Blood draws
    - Complete blood count (Final Clinic Visit)
    - Complete metabolic panel - BUN, creatinine, ALT, AST (Final Clinic Visit)
    - Syphilis RPR (Final Clinic Visit; only if indicated at Enrollment)
    - HIV-1 serology (Final Clinic Visit; only if indicated at Enrollment)
    - Plasma archive (Enrollment)
- Rectal GC/CT by NAAT (only if indicated at Enrollment, Treatment 1, Treatment 2 and Final Clinic Visit)
- Urine GC/CT by NAAT (only if indicated at Enrollment, Treatment 1, Treatment 2, and Final Clinic Visit)
- Rectal swabs for microflora (Enrollment, Treatment 1, and Final Clinic Visit)
- Rectal sponge for cytokines (Enrollment, Treatment 1, and Final Clinic Visit)
- Normosol-R enema for rectal lavage to collect effluent for epithelial sloughing and fecal calprotectin (Enrollment, Treatment 1, and Final Clinic Visit)
- Anoscopy and rectal biopsies (Enrollment, Treatment 1, and Final Clinic Visit; only if indicated at Treatment 2 visit)
- Flexible sigmoidoscopy and rectal biopsies (Enrollment, Treatment 1, and Final Clinic Visit)
- Administration of study product (Treatment 1 and Treatment 2)
- Collection of used and unused study product (Final Clinic Visit)

There will also be two follow-up phone assessments: one completed within 24 hours after the Treatment 1 Visit and the other completed within 14 days of the Final Clinic Visit. The purpose of both follow-up phone assessments is to inquire about any possible adverse events the participant may experience as a result of study product use, application or procedures performed.

6.5 Follow-up Visit Locations

All visits will be conducted at the site clinics. No study specific assessments may be completed off-site. The exceptions to this are the Follow-up Phone Assessment and the Follow-up Phone Assessment/Termination Visit. Site staff will contact the participant to evaluate if the he or she has experienced any adverse events.

6.6 Study Product Supply/Dispensing during Follow-up

Because of the nature of the short dosing period and follow-up in MTN-007, there will be no routine product re-supplies. Participants will receive an in-clinic dose at the Treatment 1 Visit as well as an 8-day supply of study product at the Treatment 2 Visit. The supply of study product at the Treatment 2 Visit encompasses the full dosing for this study (7 days) plus one extra applicator. Product re-supply will occur only in the event of lost or damaged product that must be replaced. For complete details of study product dispensing please see Section 9 of this manual.

6.7 HIV Testing during Follow-up

In addition to HIV testing at screening, another HIV test will be done at the Final Clinic Visit. The algorithm to be followed for this final test can be found in Appendix II of the protocol. Full information on the procedural and documentation requirements of the algorithm and the processing of the HIV test can be found in Section 12 of this SSP.

6.8 Modified Follow-up Procedures

Participants who permanently discontinue study product will not routinely be withdrawn from the study. Rather, every effort will be made to complete all protocol-specified visits and procedures with these participants with the following exceptions.

6.8.1 Participants Who Become Infected with HIV

Participants who become infected with HIV after enrollment will be maintained in follow-up. All participants who become infected with HIV will be counseled and referred to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons. For any participants who become HIV-infected and also become pregnant during follow-up, every effort will be made to facilitate access to interventions such as single-dose neviripine to reduce the probability of HIV transmission to the participant's infant. Study staff will capture seroconversions on study case report forms (CRFs).

While in scheduled follow-up, all protocol-specified study procedures will continue to be conducted for HIV-positive participants, with the following exceptions:

- After HIV infection is confirmed per the algorithm and the participant's enrollment plasma specimen has been tested for evidence of HIV infection, if applicable, HIV testing will be discontinued.
- Provision of study product (product use will be permanently discontinued). Site staff will make every effort to recover any unused study product immediately after the site becomes aware of the participant's HIV status.
- Protocol and Product Use Adherence Counseling

- Counseling for HIV/STI risk reduction will be modified to address primary and secondary HIV/STI prevention for infected individuals.
- Anoscopy (unless clinically indicated)
- Flexible sigmoidoscopy (unless clinically indicated)

6.8.2 Participants Who Become Pregnant

Participants who become pregnant after enrollment will be maintained in follow-up. Participants who are pregnant at the Final Clinic Visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained).

While in scheduled follow-up, all protocol-specified study procedures will continue to be conducted for pregnant participants, with the following exceptions:

- Provision of study product (product will be permanently discontinued)
- Protocol and Product Use Adherence counseling
- Rectal Exam
- Anoscopy (unless clinically indicated)
- Flexible Sigmoidoscopy (unless clinically indicated)
- Anorectal swabs
- Qualitative hCG
- Contraceptive counseling

For all participants who become pregnant, regardless of study treatment group, a Pregnancy Report and History case report form must be completed to report the pregnancy. A Pregnancy Outcome case report 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 13.6) and/or in the DAIDS Expedited Adverse Event Reporting System, as described in Section 11 of this manual. Whenever possible, pregnancy outcomes should be ascertained based on medical records or other written documentation from a licensed health care practitioner. When medical records cannot be obtained outcomes may be ascertained based on participant report.

6.8.3 Participants Who Voluntarily Discontinue Study Product

Participants who voluntarily discontinue study product after enrollment will be maintained in follow-up. Protocol-specified procedures will continue except:

- Provision of study product
- Protocol and Product Use Adherence counseling
- Anoscopy (unless clinically indicated)
- Flexible sigmoidoscopy (unless clinically indicated)

6.8.4 Participants Discontinued from Study Product by the Site Investigator

Participants who are discontinued study product by the discretion of the Site IoR after enrollment will be maintained in follow-up. All protocol-specified study procedures will continue except:

- Provision of study product (product will be permanently discontinued)
- Protocol and Product Use Adherence counseling
- Anoscopy (unless clinically indicated)
- Flexible sigmoidoscopy (unless clinically indicated)

6.9 Participant Transfers

The transfer of participants is not expected to occur in MTN-007, but the following instructions are provided should the rare participant transfer occur.

During the course of the study, participants may leave the area in which they enrolled in the study and re-locate to another area where the study is taking place. To maximize participant retention, participants who re-locate from one study location to another should be encouraged to continue their study participation at their new location. To accomplish this, study staff at both the original site (called the "transferring" site) and the new site (called the "receiving" site) will complete the process of a participant transfer.

- Upon identifying a need for a participant transfer, the transferring site will notify the receiving site as well as the MTN CORE (FHI), MTN SDMC, MTN NL and MTN Pharmacy Affairs.
- The MTN CORE (FHI) will provide further guidance for the transfer to the involved sites.

6.10 Study Exit Considerations

Procedural requirements for conducting study exit visits are specified in protocol Section 7. Further procedural guidance is incorporated in the Follow-up Phone Assessment/Termination Visit checklist in Section 7 of this manual. Provided in the remainder of this section is additional information related to key aspects of study exit visits.

6.10.1 Final Study Contacts

Although the Follow-up Phone Assessment/Termination Visit is the last scheduled study visit, a final contact may be required afterwards to provide the participant with his or her final study test results, post-test counseling, and treatment, if needed. Additional contacts also are required for:

- Participants with certain types of AEs that are ongoing at study exit
- Participants who are pregnant at study exit

Participants with positive or indeterminate HIV Western blot (WB) or Immunofluorescent antibody (IFA) as the time required to obtain all final study test results. Study staff may complete final contacts at the study site, by telephone, or at community-based locations, depending on site capacities and site and participant preferences. All final contacts must be documented in participant study records, but no case report forms are completed for these contacts.

6.10.2 HIV Counseling and Testing

HIV testing is performed at the Final Clinic Visit per the algorithm. If the WB or IFA is positive or indeterminate, additional specimen collection and testing will be required to clarify or confirm the participant's HIV status; therefore, additional visits may be required after the Final Clinic Visit. HIV pre- and post-test counseling provided at the Final Clinic Visit or the Follow-up Phone Assessment/Termination Visit should emphasize that additional counseling and testing will be provided to the participant after his or her Final Clinic Visit or Follow-up Phone Assessment/Termination Visit, if needed, to clarify or confirm his or her HIV status.

6.10.3 Study Product Completion (Gel Participants Only)

All participants randomized to receive gel are expected to complete study product use at the Final Clinic Visit. All used and unused study applicators should be collected from the participant and returned to the study clinic on the day of collection. Clinic staff will count the number of used and unused study applicators returned at the Final Clinic Visit and complete a Study Product Returns (SPR) case report form. In addition, clinic staff should add the participant's PTID to a cumulative listing of participants who have exited the study, which should be provided to pharmacy staff on a weekly basis.

Participants should be reminded to bring all used and unused product supplies to their Final Clinic Visit. In most cases this will only be 1 unused applicator and 7 used applicators returned. For participants who do not bring all used and unused supplies to their Final Clinic Visits, arrangements must be made to collect the remaining supplies as soon as possible. If the study product is not collected within five working days after the Final Clinic Visit, the MTN-007 Protocol Safety Review Team (PSRT) must be informed, using the PSRT Query Form. When informing the PSRT, please describe the reason for the product hold (i.e., study exit), actions taken to try to collect the unreturned study product, and plans and timelines for further action to collect the product.

6.10.4 AE Management and Documentation

All AE Log forms completed for each participant should be reviewed at the Final Clinic Visit as well as the Follow-up Phone Assessment/Termination Visit and updated as needed. For AEs that are ongoing at the last phone call (Follow-up Phone Assessment/Termination Visit), the status/outcome of the AE should be updated to "continuing at end of study participation" and the AE Log form should be re-faxed to SCHARP DataFax.

For any serious or expedited AEs (SAEs/EAEs) that are continuing at a participant's Follow-up Phone Assessment/Termination Visit, the IoR/designee must establish a clinically appropriate follow-up plan for the AE (see Section 11.1 of this manual for more information on SAEs and EAEs). At a minimum, the AE must be re-assessed by study staff 30 days after the participant's Follow-up Phone Assessment/Termination Visit; additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the Follow-up Phone Assessment/Termination Visit. It is recommended that AE follow-up plans be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9.

For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The MTN-007 PSRT may advise study staff as to whether any additional follow-up may be indicated on a case by case basis.

For AEs that are re-assessed after the participant's Follow-up Phone Assessment/Termination Visit, information on the status of the AE at the time of re-assessment will be recorded in source documents only. No updates should be made to AE Log case report forms based on the re-assessments. All information related to the re-assessment of AEs should be documented in the participant's chart notes, including all efforts to contact the participant.

6.10.5 Referral to Non-Study Service Providers

After completing their final study contacts, participants will no longer have routine access to services provided through the study, such as health care and HIV counseling and testing. Participants should be counseled about this, ideally before and during their Final Clinic Visits and Follow-up Phone Assessment Visits/Termination Visits, and provided information on where they can access such services after study exit. It is strongly recommended that all study sites develop a sample script that can be used when discussing this issue with exiting participants, as well as written referral sheets that can be given to participants at their Final Clinic Visit (Note: the sample scripts and referral sheets must be approved by each site's IRB/EC before they can be used).

6.10.6 Post-Study Contacts

It is expected that all participants will be re-contacted by study staff approximately three to nine months after study completion, when it is expected that study results will be available for dissemination to participants.

To facilitate post-study contact with participants, locator information should be actively reviewed and updated at all Follow-up Phone Assessment/Termination Visits, and participants should be counseled to contact the study site should their locator information change after exiting the study. In addition, participant preferences for methods to be used for contacting them when study results are available should be documented in participant study records.

Lastly, for participants whom study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the participant and documented.

Section 7. Visit Checklists

This section contains examples of checklists detailing the protocol-specified procedures that must be completed at MTN-007 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 13.

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 and product use 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.

- 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 "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 (FHI), 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 must be administered prior to HIV/STI risk reduction and protocol and product adherence counseling.

- Rectal specimens must be collected the order outlined in the rectal examination visit checklists. Rectal samples should be collected in the following order:
    1. Rectal swab for GC/CT
    2. Rectal swab for microflora
    3. Rectal sponge for cytokines
    4. Digital rectal examination
    5. Rectal lavage/effluent for epithelial sloughing
    6. Stool sample for fecal calprotectin
    7. *Flexible sigmoidoscopy and biopsies at 15 cm for Histology, Cytokine RT PCR, Mucosal T cell phenotyping, and mucosal gene expression array
    8. *Anoscopic biopsies at 9 cm for Histology, Cytokine RT PCR, Mucosal T cell phenotyping, and mucosal gene expression array

*Note: If at anytime the collection of biopsies is limited, rectal biopsies should be collected in the following order of importance:

1. Histology
2. Mucosal Gene Expression Array
3. Cytokine RT PCR
4. Mucosal T Cell Phenotyping.

Screening Visit

PTID:	Visit Date:	Visit Code: 1.0

1. _____ Confirm whether the participant is ≥ 18 years of age. Explain the two-step (screening and enrollment) informed consent process.

2. _____ Confirm participant identity. Cross-check with the MTN-007 Participant Name-PTID Link Log to determine whether a MTN-007 Participant ID number has previously been assigned to the participant.

3. _____ Explain the content and sequence of procedures for the remainder of the visit.

4. _____ Obtain locator information and record on site specific 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 he/she is ineligible. Retain documentation completed thus far, and complete the form, but do not fax any forms to SCHARP.

5. _____ Review consent with participant according to local SOPs.

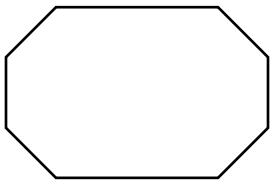
6. _____ Administer and obtain screening informed consent with participant. Complete Consent Process Coversheet.

   If the participant does not consent to screening, STOP. Inform the participant that he/she is ineligible.

7. _____ Assign an MTN-007 PTID (if not done during a previous screening attempt) by completing a new row in the MTN-007 Name-PTID Link Log.

8. _____ Complete the **Screening Consent** 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** CRF.

PTID:	Visit Date:	Visit Code: 1.0

10. _____ Collect approximately 15-60 mL urine and:

- 10a. _____ Aliquot approximately 5-10 mL for qualitative pregnancy ***(for females of childbearing potential only)*** and dipstick urinalysis tests.
- 10b. _____ Complete testing logs and record result on the **Screening Visit Eligibility** (non-DataFax) CRF.
- 10c. _____ Complete dipstick urinalysis and record results for protein, glucose, nitrites, and leukocytes according to local SOP and on **Laboratory Results** CRF. If dipstick urinalysis is positive for leukocytes or nitrites, provide treatment and/or additional UTI work-up per site SOP. Document treatment and/or additional work-up in chart notes.
- 10d. _____ Prepare remaining urine for gonorrhea and chlamydia NAAT. Record results on **STI Laboratory** CRF when available.

If the participant is pregnant, STOP. Inform the participant that she is ineligible. Retain documentation completed thus far. Do not fax any forms to SCHARP.

11._____ Assess behavioral eligibility by administering the **Screening Visit Eligibility** (non-DataFax) CRF.

12._____ Provide HIV pre-test, HIV/STI risk reduction and condom counseling. Provide study-specific male condoms. ***(Sites may choose to provide condoms at the end of the visit)***.

13._____ Collect blood:

- □ Plain tube (no additive)
- □ EDTA

14._____ Prepare blood for testing at the local lab:

- □ HIV-1 serology
- □ Syphilis RPR
- □ HSV-1 and HSV-2 serology
- □ CBC with differential and platelets
- □ BUN, creatinine, Calculated creatinine clearance, ALT, AST
- □ Hepatitis B Surface Antigen

Tailor this item to reflect site-specific tube types and volumes.

15. _____ Obtain medical history with documentation of current medications. Record on **Participant Reported Baseline Medical and Menstrual History** form (non-Data Fax, pages 7-8 completed only for females), and **Concomitant Medications Log** CRF.

PTID:	Visit Date:	Visit Code: 1.0

16. _____ Provide contraceptive counseling and [prescribe/provide/refer for] contraception, if applicable and document in chart notes.

17. _____ Perform Physical Exam per protocol section 7.11 and record findings on the **Physical Exam** (non-DataFax) CRF.

18. _____ Perform and document rectal exam using the *Screening Rectal Exam Checklist*. Record findings on the **Rectal Exam** CRF.

19. _____ Evaluate findings identified during rectal and physical examinations and medical and menstrual history review. Refer for or provide any clinically indicated treatment; document in chart notes and update **Concomitant Medications Log** CRF, if applicable. Assess clinically eligibility by completing the **Medical Eligibility** (non-DataFax) CRF.

NOTE: Medical Eligibility (non-DataFax) CRF will be completed at screening but finished at enrollment, when all labs and medical/clinical information are available.

20. _____ 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.

21. _____ Schedule the Enrollment Visit, taking into account the timing for receipt of test results and the 36-day screening period.

22. _____ Provide reimbursement.

23. _____ Complete the **Pre-Existing Conditions** CRF. Record all medical conditions that are ongoing at the time of screening, based on source data collected throughout the screening process.

Note: Whenever possible, record a diagnosis rather than individual signs and symptoms. When this is not possible, record each individual sign or symptom. 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 screening.

24. _____ Document the visit in a signed and dated chart note.

25. _____ Complete and review all other participant chart contents for the visit, but do not fax any forms to SCHARP DataFax.

Screening Visit

PTID:	Visit Date:	Visit Code: 1.0

*NOTE: The **STI Laboratory Results** and **Laboratory Results** CRFs (and **HIV Test Results** CRF) should be completed when all required test results are available, prior to the Enrollment Visit. Do not fax any forms to SCHARP until the participant is randomized. If the participant is deemed ineligible, retain all DataFax forms on site but do not fax any of them to SCHARP.*

Screening Rectal Exam

PTID:	Visit Date:	Visit Code: 1.0

1. _____ Review chart notes and other relevant documentation.

2. _____ Affix a SCHARP-provided PTID label to the required primary tube at the time of collection. Record PTID and 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 the participant in a lateral position on the left side. Drape the participant comfortably.

5. _____ Inspect the anus and surrounding region visually. Document abnormal findings on items # 1-1a of the **Rectal Exam** CRF and in chart notes.

6. _____ Use study specified lubricant to lubricate the anoscope. Gently insert anoscope into the rectum (until the lateral 'wings' touch the anal margin). Remove the obturator.

7. _____ Collect the rectal swab for GC/CT testing by removing it from the plastic tube and inserting through the anoscope placing in contact with the rectal wall. Gently turn the swab 360 degrees and remove. Place the rectal swab in the transport tube, break off shaft of swab and cap.

8. _____ Slowly and gently remove anoscope.

9. _____ Perform a digital rectal examination by inserting a gloved finger, lubricated with study specified lubricant, into the anal canal and sweep around the internal anal circumference. Document abnormal findings on items #2-2a of the **Rectal Exam** CRF. Any unexpected discomfort should also be documented in chart notes and/or in the comments field of the Rectal Exam CRF.

10. _____ Evaluate any abnormalities for eligibility.

Enrollment Visit

PTID:	Visit Date:	Visit Code: 2.0

1. _____ Complete participant registration, confirm the participant's identity, and verify PTID per site SOPs.

2. ____ Review and/or update locator information.

3. _____ Confirm that the 36-day window has not been exceeded for the current screening attempt.

4. _____ Review chart notes and other relevant documentation from previous visit(s). Provide test results from previous visit(s), if applicable.

5. _____ Confirm the participant's behavioral and clinical eligibility status based on all screening documentation. Complete the **Enrollment Visit Eligibility** (non-DataFax) CRF.

6. _____ Provide HIV test results in the context of post-test counseling. [Before disclosing result(s) to participant, obtain independent review, verification, and sign-off of results(s)]. Provide referrals if needed/requested. Explain the participant's current study eligibility status.

If the participant is HIV-positive per protocol Appendix II, STOP. Provide appropriate post-test counseling, and inform the participant that he/she is ineligible. Refer to local care providers for follow-up and treatment of HIV. Retain documentation completed thus far but do not fax any forms to SCHARP.

7. _____ Explain again the two-step informed consent process and obtain written informed consent for enrollment into the study. Document the informed consent process in a chart note and on any other documents per site SOP. Complete Consent Process Coversheet.

If the participant does not consent to the study, STOP. Retain documentation completed thus far, but do not fax any forms to SCHARP.

8. _____ Administer assessment of informed consent comprehension, utilizing comprehension checklist, per site SOP

9. _____ 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 Coversheet.

Consent for specimen storage and possible future research testing is <u>optional</u>. If the participant does not consent, he/she may still take part in the study.

Enrollment Visit

PTID:	Visit Date:	Visit Code: 2.0

10. _____ Complete items 1-3 of the **Enrollment** CRF.

11. _____ Collect 15-60 mL urine:

11a. _____ Aliquot approximately 5-10 mL and perform qualitative pregnancy test ***(For females of childbearing potential only)***

11b. _____ Complete testing logs and record result on the **Medical Eligibility** (non-DataFax) CRF.

If the participant is pregnant, STOP. Inform the participant that she is ineligible. Retain documentation completed thus far. Do not fax any forms to SCHARP.

11c. _____ If clinically indicated, prepare remaining urine for gonorrhea and chlamydia NAAT. Record results on **STI Laboratory Results** CRF when available.

12. _____ Review/update the **Participant-reported Baseline Medical and Menstrual History** (non-DataFax) CRF (pages 7-8 are for females only)and **Concomitant Medications Log**, including family planning methods as necessary. Document review with a signed and dated note on each document reviewed. Initial and date updated entries.

13. _____ Provide contraceptive counseling and [prescribe/ provide/refer] for contraception, if applicable.

14. _____ Perform the physical exam as per Protocol Section 7.11 and record findings on the **Physical Exam** (non-DataFax) form.

15. _____ Provide HIV pre-test counseling if clinically indicated. Collect blood. (Specimen collection must occur prior to randomization)

- ☐ Plain tube (no additive)
- ☐ EDTA

16. _____ Prepare blood for testing at the local lab:

- ☐ **Plasma archive**
- ☐ Syphilis RPR (if clinically indicated)
- ☐ HIV Serology (if clinically indicated)

Tailor this item to reflect site-specific tube types and volumes.

17. _____ Perform and document rectal exam using the *Enrollment Visit Rectal Exam Checklist*. Record findings on the **Rectal Exam** CRF.

18. _____ Evaluate findings identified during rectal and physical examinations and medical and menstrual history review. Refer for or provide any clinically indicated treatment; document in chart notes and update **Concomitant Medications Log** CRF, if applicable.

19. _____ Administer the **CASI Baseline Behavioral Questionnaire (BBQ)**. Complete item 7 of the **Enrollment** CRF.

This must be administered prior to HIV/STI risk reduction counseling as well as random assignment

20. _____ **Randomization procedures:**
For Non-Replacement Participants Only: obtain the next sequential MTN-007 Clinic Randomization Envelope and assign it to the participant per site SOPs.

Replacement Participants Only: obtain the study notebook and prescriptions for the participant being replaced. Based on the randomization assignment of the participant being replaced (completed yellow copy of prescription), obtain the appropriate blank MTN-007 replacement prescription. Transcribe all of the randomization information from the pre-printed MTN-007 Prescription of the participant being replaced onto the blank MTN-007 replacement prescription.

21. _____ Inform the participant of his/her assignment ["gel" or "no treatment (no gel)"].

21a. _____ ***Participants assigned to "no treatment (no gel)":*** Complete the prescription and deliver the top (white) copy of the completed prescription to the pharmacy and store the bottom (yellow) copy and opened envelope in the participant's study notebook.

21b. _____ ***Participants assigned to "gel":*** Store both prescriptions and the opened envelope in the participant's study notebook. The single dose gel prescription will be completed and delivered to the pharmacy at the Treatment 1 Visit. The seven-day gel prescription will be completed and delivered to the pharmacy at the Treatment 2 Visit.

22. _____ Provide HIV/STI risk reduction and male condom counseling. Provide counseling related to the importance of participant's study participation and product use. Provide protocol adherence counseling. Provide study condoms and lubricant. Emphasize the unknown effectiveness of the study products and the importance of condom use for protection against HIV.

Enrollment Visit

PTID:	Visit Date:	Visit Code: 2.0

23. _____ Complete the remainder of the **Enrollment** CRF.

24. _____ Reinforce site contact information and instructions to contact the site to report symptoms and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.

25._____ Explain the follow-up visit schedule to the participant and schedule Treatment 1 Visit. Inform the participant of tests to be performed at the next visit.

26. _____ Provide reimbursement for study visit.

27. _____ Review/update **Pre-existing Conditions** CRF. Record all medical conditions that are ongoing at the time of participant randomization, based on source data collected throughout the screening and enrollment process.

28._____ Document the visit in a signed and dated chart note.

29. _____ Complete and review all participant chart contents from both the screening and enrollment visits, including the following non-DataFax forms:

- ☐ Screening Visit Eligibility
- ☐ Enrollment Visit Eligibility
- ☐ Medical Eligibility
- ☐ Participant-reported Baseline Medical and Menstrual History
- ☐ Physical Exam (completed at the Screening Visit)
- ☐ Physical Exam (completed at the Enrollment Visit)
- ☐ LDMS Specimen Tracking Sheet

30. _____ Fax all <u>required</u> DataFax CRFs to SCHARP:

- ☐ Demographics
- ☐ Screening Consent
- ☐ Rectal Exam (completed at the Screening Visit)
- ☐ STI Laboratory Results
- ☐ Laboratory Results
- ☐ Concomitant Medications Log
- ☐ Pre-existing Conditions
- ☐ Rectal Exam (completed at the Enrollment Visit)
- ☐ Enrollment
- ☐ Anoscopy and Sigmoidoscopy Results
- ☐ Specimen Storage

Enrollment Rectal Exam

PTID:	Visit Date:	Visit Code: 2.0

1. _____ Review chart notes and other relevant documentation.

2. _____ Explain the exam procedures to the participant and answer any participant questions.

3. _____ Affix a SCHARP-provided PTID label to the specimen collection tubes at the time of collection. Record the PTID and write the specimen collection date in ink on the label.

4. _____ Position the participant in a lateral position on the left side. Drape the participant comfortably.

5. _____ Inspect the anus and surrounding region visually. Document abnormal findings on items # 1-1a of the **Rectal Exam** CRF and in chart notes.

6. _____ Use study provided lubricant to lubricate the anoscope. Gently insert the anoscope into the rectum (until the lateral 'wings' touch the anal margin). Remove the obturator.

7. ____ If clinically indicated, collect the rectal swab for GC/CT testing by removing it from the plastic tube and inserting it through the anoscope placing in contact with the rectal wall. Gently turn the swab 360 degrees and remove. Place the rectal swab in the transport tube, break off shaft of swab and cap.

8. _____ Collect the rectal swab for Microflora by inserting the swab through the anoscope and place in contact with the rectal wall. Gently turn the swab 360 degrees gently and remove from rectum. Slowly remove the swab and place into a transport tube (labeled with a SCHARP-provided label), submerging the swab into the gel. Break off the shaft of the swab and cap

9. _____ Collect the rectal sponge for Cytokines by inserting the sponge through the anoscope and place in contact with the rectum (approximately 9 cm in the rectum). *The sponge should remain in place for five minutes*.

10. _____ Remove rectal sponge and place in a specimen collection tube (labeled with a SCHARP-provided label). Slowly remove anoscope.

11. _____ Perform a digital rectal examination by inserting a gloved finger, lubricated with study specified lubricant, into the anal canal and sweep around the internal anal circumference. Document abnormal findings on items #2-2a of the **Rectal Exam** CRF. Any unexpected discomfort should also be documented in chart notes and/or in the comments field of the **Rectal Exam** CRF.

Enrollment Rectal Exam

PTID:	Visit Date:	Visit Code: 2.0

12. _____ Position specimen pan provided in the Genova Diagnostic Calprotectin Kit onto available toilet.

13. _____ Prepare appropriate pre-packaged enema bottle for **rectal lavage** and apply a small amount of study specified lubricant to the tip of the enema bottle. Gently insert enema bottle into the rectum and and slowly dispell the fluid into the rectum.

Instruct participant to hold the fluid in the rectum for approximately 3-5 minutes then expel it, including stool, into the specimen pan placed over the toilet.

14. _____ Transfer stool sample for **fecal calprotectin** with the flat wooden stick provided in the Genova Diagnostics-provided kit into the white top vial and prepare for transport.

15. _____ Transfer effluent for assessment of **epithelial sloughing** to a conical tube for initial processing and prepare per Section 12 of the SSP for shipment to the MTN Network Lab.

16. _____ Re-position the participant in a lateral position on the left side. Drape the participant comfortably.

17. _____ Use study provided lubricant to lubricate the tip of the sigmoidoscope. Insert the sigmiodoscope into the anal canal.

18. _____ Using the jumbo endoscopic foreceps, collect seven rectal biopsies at approximately 15 cm from the anal verge via flexible sigmoidoscopic biopsy. Remove sigmoidoscope following specimen collection.

19. _____ Use study provided lubricant to lubricate the anoscope. Insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge.
Remove the obturator.

20. _____ Using the jumbo endoscopic foreceps, collect seven rectal biopsies at approximately 9 cm from the anal verge via **anoscopic** biopsy. Remove anoscope following specimen collection.

Enrollment Rectal Exam

PTID:	Visit Date:	Visit Code: 2.0

Note: Required biopsies are to be collected as follows:

_____1 biopsy at each location for Histology (15 cm and 9 cm)
_____2 biopsies at each location for Cytokine RT PCR (15 cm and 9 cm)
_____3 biopsies at each location for Mucosal T Cell Phenotyping (15 cm and 9 cm)
_____1 biopsy at each location for Mucosal Gene Expression Array. (15 cm and 9 cm)

21. _____ Obtain vital signs and document in chart notes. Evaluate any abnormal findings

22. _____ Document exam findings on the **Anoscopy and Sigmoidoscopy Results** CRF. Document specimen collection and storage on the **Specimen Storage** CRF and the **LDMS Specimen Tracking Sheet (**non-Datafax) CRF.

Treatment 1 Visit

PTID:	Visit Date:	Visit Code: 3.0

1. _____ Confirm the participant's identity, and verify PTID per site SOPs.

2. _____ Review and/or update locator information.

3. _____ Review chart notes and other relevant documentation from previous visit(s). Provide test results from previous visit(s), if applicable.

4. _____ Explain the content and sequence of procedures for today's visit. Review elements of informed consent as needed.

5. _____ Collect 15-60 mL urine and:
   - 5a. _____ Aliquot approximately 5-10 mL and perform qualitative pregnancy test **(For females of childbearing potential only)**
   - 5b. _____ Complete testing logs and record result on the **Follow-Up Visit/Phone Call** CRF.
   - 5c. _____ If clinically indicated, prepare remaining urine for gonorrhea and chlamydia NAAT. Record results on **STI Laboratory Results** CRF, when available.

   If the participant is pregnant, modify remaining study visit procedures per protocol section 7.8.2. If the participant is pregnant and is randomized to gel arm:
   - 5d. _____ Inform the participant that she will be discontinued from the study product use and will not be provided with any study gel.
   - 5e. _____ Complete a **Pregnancy Report and History** CRF and a **Product Hold/Discontinuation Log** CRF.

6. _____ Perform interval medical/menstrual history; record findings on the **Participant Reported Follow-up Medical and Menstrual History** form. Review and update the **Concomitant Medications Log** (including family planning methods) as necessary.

7. _____ Provide contraceptive counseling and [provide and/or refer] for contraception, if applicable.

8. _____ Perform physical exam per Protocol Section 7.11 and record findings on the **Physical Exam** (non-DataFax) form.

9. _____ Perform and document rectal exam using the *Treatment 1 Visit Rectal Exam Checklist*. Record findings on the Rectal Exam CRF.

Treatment 1 Visit

PTID:	Visit Date:	Visit Code: 3.0

10. _____ Evaluate findings identified during rectal and physical examinations and medical and menstrual history review. Refer for or provide any clinically indicated treatment; document in chart notes and update **Concomitant Medications Log** CRF, if applicable.

11._____ **ASSESS ELIGIBILITY TO CONTINUE PRODUCT USE BASED ON INTERVAL MEDICAL/MENSTRUAL HISTORY AND RECTAL EXAM FINDINGS**

NOT ELIGIBLE (Gel Participants Only): Refer to Protocol Section 9.4 and the SSP Manual, Section 10, for guidelines on holding or discontinuing study product. Contact PSRT if there are any questions.

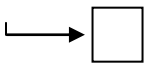
11a. _____ If product use is discontinued at this visit, document the rationale in chart notes and/or on other applicable source documents. Complete the **Product Hold/Discontinuation Log** and a **Study Gel Request Slip** to inform the site's pharmacist of the product discontinuation.

11b. _____ Deliver the white copy of the completed Study Gel Request Slip to the pharmacy; retain the yellow copy in the participant's study notebook.

ELIGIBLE (Gel Participants Only): Request single dose of study product from pharmacy.

11a. _____ Follow site-specific procedure for product supply. Complete the MTN 007 Prescription – Single Dose Gel ("replacement prescription – gel" for gel replacement participants). Record the participant ID and mark if written informed consent was provided.

11b. _____ Deliver completed white copy to the pharmacy. The original prescription must be delivered to the pharmacist in order for the study product to be dispensed. The yellow copy of the prescription will be retained in the participant's study notebook.

11c. _____ After product supply is received, document the number of applicators provided here 

12. _____ Provide HIV/STI risk reduction, protocol adherence, product use adherence, and condom counseling. Provide study-provided male condoms and lubricant.

13. _____ Explain the follow up schedule to the participant and schedule the Treatment 2 Visit and inform the participant of what to expect.

Treatment 1 Visit

PTID:	Visit Date:	Visit Code: 3.0

14. _____ Remind the participant about the Follow-up Phone Assessment that must occur within 24 hours of this visit.

15. _____ 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, contraceptive counseling, and/or condoms, if needed, prior to the next visit.

16. _____ Provide study reimbursement

17. _____ Complete **AE Log** form(s), if required, based on interval medical/menstrual history, clinical exams/assessments, and lab tests when available.

18. _____ Complete the **Follow-up Visit/Phone Call** CRF.

19. _____ Document the visit in a signed and dated chart note. Complete and review all participant chart contents for the visit, including the following non-DataFax forms:

- ☐ Physical Exam
- ☐ Participant-reported Follow-up Medical and Menstrual History
- ☐ LDMS Specimen Tracking Sheet

20._____ Fax all <u>required</u> DataFax CRFs to SCHARP:

- ☐ Rectal Exam
- ☐ Anoscopy and Sigmoidoscopy results
- ☐ Follow-up Visit/Phone Call
- ☐ Specimen Storage

If applicable:

- ☐ Adverse Experience Log
- ☐ HIV Test Results
- ☐ Missed Visit
- ☐ Pregnancy Outcome
- ☐ Pregnancy Report and History
- ☐ STI Laboratory Results
- ☐ Concomitant Medications Log
- ☐ Product Hold/Discontinuation Log

Treatment 1 Visit Rectal Exam

PTID:	Visit Date:	Visit Code: 3.0

1. _____ Review chart notes and other relevant documentation.

2. _____ Explain the exam procedures to the participant and answer any participant questions.

3. _____ Affix a SCHARP-provided PTID labels to the specimen collection tubes at the time of collection. Record the PTID and write the specimen collection date in ink on the label.

4. _____ Position the participant in a lateral position on the left side. Drape the participant comfortably.

5. _____ Inspect the anus and surrounding area visually. Document abnormal findings on items # 1-1a of the **Rectal Exam** CRF and in chart notes.

6. _____ If clinically indicated, lubricate the anoscope with the study specified lubricant and insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

7. _____ If clinically indicated, collect the rectal swab for GC/CT testing by removing it from the plastic tube and inserting it through the anoscope placing in contact with the rectal wall. Gently turn the swab 360 degrees and remove. Place the rectal swab in the transport tube, break off shaft of swab and cap. Slowly remove anoscope.

8. _____ **ELIGIBLE (Gel Participants Only):** Under the observation of the study clinician, instruct participant to self-administer the single dose of study gel.

9. _____ Lubricant the anoscope with the study specified lubricant and insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

10. _____ Collect the rectal swab for **Microflora** by inserting the swab through the anoscope and place in contact with the rectal wall. Gently turn the swab 360 degrees gently and remove from rectum. Slowly remove the swab and place into a transport tube (labeled with a SCHARP-provided label), submerging the swab into the gel. Break off the shaft of the swab and cap.

11. _____ Collect the rectal sponge for **Cytokines** by inserting the sponge through the anoscope and place in contact with the rectum (approximately 9 cm in the rectum). *Note: The sponge should remain in place for five minutes*.

Treatment 1 Visit Rectal Exam

PTID:	Visit Date:	Visit Code: 3.0

12. _____ Remove rectal sponge and place in a specimen collection tube (labeled with a SCHARP-provided label). Slowly remove anoscope.

13. _____ Perform a digital rectal examination by inserting a gloved finger, lubricated with study specified lubricant, into the anal canal and sweep around the internal anal circumference. Document abnormal findings on items #2-2a of the **Rectal Exam** CRF. Any unexpected discomfort should also be documented in chart notes and/or in the comments field of the **Rectal Exam** CRF.

14. _____ Position specimen pan provided in the Genova Diagnostic Calprotectin Kit onto available toilet.

15. _____ Prepare appropriate pre-packaged enema bottle for **Rectal Lavage** by applying a small amount of study specified lubricant to the tip of the enema bottle. Gently insert enema bottle into the rectum and and slowly dispell the fluid into the rectum.

Note: Instruct participant to hold the fluid in the rectum for approximately 3-5 minutes then expel it, including stool, into the specimen pan placed over the toilet.

16. _____ Transfer stool sample for **fecal calprotectin** with the flat wooden stick provided in the Genova Diagnostics-provided kit into the white top vial and prepare for transport.

17. _____ Transfer effluent for assessment of **epithelial sloughing** to a conical tube for initial processing and prepare per Section 12 of the SSP for shipment to the MTN Network Lab.

18. _____ Re-position the participant in a lateral position on the left side. Drape the participant comfortably.

19. _____ Use study provided lubricant to lubricate the tip of the sigmoidoscope. Insert the sigmiodoscope into the anal canal.

20. _____ Using the jumbo endoscopic foreceps, collect seven rectal biopsies at approximately 15 cm from the anal verge via flexible sigmoidoscopic biopsy. Remove sigmoidoscope following specimen collection.

21. _____ Use study provided lubricant to lubricate the anoscope. Insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

Treatment 1 Visit Rectal Exam

PTID:	Visit Date:	Visit Code: 3.0

22. _____ Using the jumbo endoscopic forceps, collect seven rectal biopsies at approximately 9 cm from the anal verge via **anoscopic** biopsy. Remove anoscope following specimen collection.

Note: Required biopsies are to be collected as follows within 30 minutes of gel application:
_____1 biopsy at each location for Histology (15 cm and 9 cm)
_____2 biopsies at each location for Cytokine RT PCR (15 cm and 9 cm)
_____3 biopsies at each location for Mucosal T Cell Phenotyping (15 cm and 9 cm)
_____1 biopsy at each location for Mucosal Gene Expression Array (15 cm and 9 cm)

23. _____ Obtain vital signs and document in chart notes. Evaluate any abnormal findings.

24. _____ Document exam findings on the **Anoscopy and Sigmoidoscopy Results** CRF. Document specimen collection and storage on the **Specimen Storage** CRF and the **LDMS Specimen Tracking Sheet** (non-DataFax) CRF.

Follow-Up Phone Assessment
(24 hours After Treatment 1 Visit)

PTID:	Visit Date:	Visit Code: 4.0

1. _____ Confirm the participant's identity and verify PTID per site SOPs.

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 phone assessment.

5. _____ Inquire about any AEs the participant may have experienced as a result of study product or procedures performed during the Treatment 1 Visit.

6. _____ Refer for follow-up care as needed. Document follow-up in chart notes. If required based on all available information, complete **AE Log** CRF and/or **Product Hold/Discontinuation Log** CRF.

7. _____ 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, contraceptive counseling, and/or condoms, if needed, prior to the next visit.

8. ____ Complete **Follow-up Visit/Phone Call** CRF.

9. _____ Document the visit in a signed and dated chart note. Complete and review case report forms for the visit.

10. _____ Fax all <u>required</u> DataFax forms to SCHARP:
    - ☐ Follow-up Visit/Phone Call

    If applicable:
    - ☐ Adverse Experience Log
    - ☐ Missed Visit
    - ☐ Product Hold/Discontinuation Log

Additional Comments:

_____
_____
_____
_____
_____

Treatment 2 Visit

PTID:	Visit Date:	Visit Code: 5.0

1. _____ Confirm the participant's identity and verify PTID per site SOPs.

2. _____ Review/update locator information.

3. _____ Review chart notes and other relevant documentation from previous visit(s). Provide test results from previous visit(s), if applicable.

4. _____ Review elements of informed consent as needed. Explain the content and sequence of procedures for today's visit.

5. _____ Collect 15-60 mL urine and:

   5a. _____ Aliquot approximately 5-10 mL and perform qualitative pregnancy test ***(For females of childbearing potential only)***

   5b. _____ Complete testing logs and record result on the **Follow-Up Visit/Phone Call** CRF.

   5c. _____ If clinically indicated, prepare remaining urine for gonorrhea and chlamydia NAAT. Record results on **STI Laboratory Results** CRF, when available.

   If the participant is pregnant, modify remaining study visit procedures per protocol section 7.8.2. If the participant is pregnant and is randomized to gel arm:

   5d. _____ Inform the participant that she will be discontinued from the study product use and will not be provided with any study gel.

   5e. _____ Complete a **Pregnancy Report and History** CRF and a **Product Hold/Discontinuation Log** CRF.

6._____ Perform interval medical/menstrual history; record findings on the **Participant Reported Follow-up Medical and Menstrual History** (non-DataFax) CRF. Review and update the **Concomitant Medications Log** (including family planning methods) as necessary.

7. _____ Provide contraceptive counseling and [provide and/or refer for] contraception, if applicable.

8._____ If clinically indicated, perform physical exam as per Protocol Section 7.11. Record findings on the Physical Exam (non-DataFax) CRF.

9. _____ If clinically indicated, perform and document rectal exam using the *Treatment 2 Visit Rectal Exam Checklist*. Record findings on the **Rectal Exam** CRF.

Treatment 2 Visit

PTID:	Visit Date:	Visit Code: 5.0

10. _____ Evaluate findings identified during rectal and physical examinations and medical and menstrual history review. Refer for or provide any clinically indicated treatment; document in chart notes and update **Concomitant Medications Log** CRF, if applicable.

11._____ **ASSESS ELIGIBILITY TO CONTINUE PRODUCT USE BASED ON INTERVAL MEDICAL/MENSTRUAL HISTORY AND RECTAL EXAM FINDINGS, IF APPLICABLE**

NOT ELIGIBLE (Gel Participants Only): Refer to Protocol Section 9.4 and the SSP Manual, Section 10, for guidelines on discontinuing study product. Contact the PSRT if there are any questions.

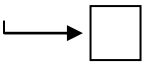
11a. _____ If product use is discontinued at this visit, document the rationale in chart notes and/or on other applicable source documents. Complete the **Product Hold/Discontinuation** Log and a **Study Gel Request** Slip to inform the site's pharmacist of the product discontinuation.

11b. _____ Deliver the white copy of the completed Study Gel Request Slip to the pharmacy; retain the yellow clinic copy in the participant's study notebook.

ELIGIBLE (Gel Participants Only): Request a seven day supply of study product from pharmacy:

11a. _____ Follow site-specific procedures for product supply. Complete the MTN 007 Prescription - Seven Day Gel ("replacement prescription – gel" for replacement participants). Record the participant's ID (PTID) on the prescription.

11b. _____ Deliver completed white copy to the pharmacy. The original prescription must be delivered to the pharmacist in order for the study product to be dispensed. The yellow copy of the prescription will be retained in the participant's study notebook.

11c. _____ After product supply is received, document the number of applicators provided here 

12. _____ **Gel Participants Only:** Provide instructions on the use of the Phone Reporting System (PRS). Provide product use counseling.

Treatment 2 Visit

PTID:	Visit Date:	Visit Code: 5.0

13. _____ Provide counseling related to the importance of study participation. Provide HIV/STI risk education, protocol adherence, and male condom counseling. Provide male condoms and lubricant. Provide referrals if needed/requested. Emphasize the unknown effectiveness of the study product and the importance of condom use for protection against HIV.

14. _____ Explain the follow-up visit schedule to the participant and schedule Final Clinic Visit and inform the participant of what to expect.

15. _____ Reinforce site contact information and instructions to contact the site to report symptoms – especially rectal symptoms – and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.

16._____ Provide study reimbursement.

17._____ Complete **AE Log** CRF, if required, based on interval medical/menstrual history, clinical exams/assessments, and lab tests when available.

18. ____ Complete **Follow-up Visit/Phone Call** CRF.

19. _____ 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:

- ☐ Participant-reported Follow-up Medical and Menstrual History
- ☐ LDMS Tracking Sheet, *if applicable*
- ☐ Physical Exam, *if applicable*

20._____ Fax all <u>required</u> Data Fax forms to SCHARP:

- ☐ Follow-up Visit/Phone Call

<u>If applicable</u>:

- ☐ Adverse Experience Log
- ☐ Anoscopy and Sigmoidoscopy Results
- ☐ Concomitant Medications Log
- ☐ HIV Test Results
- ☐ Missed Visit
- ☐ Pregnancy Outcome
- ☐ Pregnancy Report and History
- ☐ Product Hold/Discontinuation Log
- ☐ Rectal Exam
- ☐ Specimen Storage
- ☐ STI Laboratory Results

Treatment 2 Visit Rectal Exam

PTID:	Visit Date:	Visit Code: 5.0

Mark "Not applicable or N/A" next to all procedures that are not clinically indicated for the visit.

1. _____ Review chart notes and other relevant documentation.

2. _____ Explain the exam procedures to the participant and answer any participant questions.

3. _____ Affix a SCHARP-provided PTID labels to the specimen collection tubes at the time of collection. Record the PTID and write the specimen collection date in ink on the label.

4. _____ Position the participant in a lateral position on the left side. Drape the participant comfortably.

5. _____ Inspect the anus and surrounding area visually. Document abnormal findings on items # 1-1a of the **Rectal Exam** CRF and in chart notes.

6. _____ If clinically indicated, lubricate the anoscope with the study specified lubricant and insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

7. _____ If clinically indicated, collect the rectal swab for GC/CT testing by removing it from the plastic tube and inserting it through the anoscope placing in contact with the rectal wall. Gently turn the swab 360 degrees and remove. Place the rectal swab in the transport tube, break off shaft of swab and cap.

8. _____ Perform a digital rectal examination by inserting a gloved finger, lubricated with study specified lubricant, into the anal canal and sweep around the internal anal circumference. Document abnormal findings on items #2-2a of the **Rectal Exam** CRF. Any unexpected discomfort should also be documented in chart notes and/or in the comments field of the **Rectal Exam** CRF.

9. _____ If clinically indicated, use study specified lubricant to lubricate the anoscope. Insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

10. _____ Using the jumbo endoscopic foreceps, collect seven rectal biopsies at approximately 9 cm from the anal verge via **anoscopic** biopsy. Remove anoscope following specimen collection.

Treatment 2 Visit Rectal Exam

PTID:	Visit Date:	Visit Code: 5.0

Mark "Not applicable or N/A" next to all procedures that are not clinically indicated for the visit.

Note: Required biopsies are to be collected as follows:
_____1 biopsy (9 cm) for Histology
_____2 biopsies (9 cm) for Cytokine RT PCR
_____3 biopsies (9 cm) for Mucosal T Cell Phenotyping
_____1 biopsy (9 cm) for Mucosal Gene Expression Array.

11. _____ Obtain vital signs and document in chart notes. Evaluate any abnormal findings.

12. _____ Document exam findings on the **Anoscopy and Sigmoidoscopy Results** CRF. Document specimen collection and storage on the **Specimen Storage** CRF and the **LDMS Specimen Tracking Sheet** (non-DataFax) CRF.

Final Clinic Visit

PTID:	Visit Date:	Visit Code: 6.0

1. _____ Confirm the participant's identity and verify PTID per site SOPs.

2. _____ Review/update locator information.

3. _____ Review chart notes and other relevant documentation from previous visit(s). Provide test results from previous visit(s), if applicable.

4. _____ Review elements of informed consent as needed. Explain the content and sequence of procedures for today's visit.

5._____ Collect 15-60 mL urine and:

- 5a. _____ Aliquot approximately 5-10 mL for qualitative pregnancy ***(for females of childbearing potential only)*** and dipstick urinalysis tests.
- 5b. _____ Complete testing logs and record result on the **Follow Up Visit/Phone Call** CRF.
- 5c. _____ Complete dipstick urinalysis and record results for protein, glucose, nitrites, and leukocytes according to local SOP and on **Laboratory Results** CRF. If dipstick urinalysis is positive for leukocytes or nitrites, provide treatment and/or additional UTI work-up per site. Document treatment and/or additional work-up in chart notes. Update Concomitant Medications Log if necessary
- 5d. _____ If clinically indicated, prepare remaining urine for gonorrhea and chlamydia NAAT. Record results on **STI Laboratory Results** CRF, when available.

If the participant is pregnant, modify remaining study visit procedures per protocol section 7.8.2. If the participant is pregnant and is randomized to gel arm:

- 5e. _____ Complete a **Pregnancy Report and History** CRF.

6. _____ ***Gel Participants Only*****:** Collect used and unused study product. Document product collection in the chart notes. If participant did not bring the unused product at this visit, make arrangements to collect the product. Complete **Study Product Returns** CRF.

7. _____ Perform interval medical/menstrual history; record findings on the **Participant Reported Follow-up Medical and Menstrual History** (non-DataFax) CRF. Review and update the **Concomitant Medications Log** CRF (including family planning methods) as necessary

Final Clinic Visit

PTID:	Visit Date:	Visit Code: 6.0

8. _____ Perform the physical exam as per protocol section 7.11 and record findings on the **Physical Exam** (non-DataFax) CRF.

9. _____ ***Gel Participants Only*:** Administer **Product Acceptability Questionnaire**.

10. _____ Provide HIV pre-test, HIV/STI risk reduction and condom counseling. Provide study-specific male condoms. Provide referrals if needed/requested.

11._____ Collect blood:
- □ Plain tube (no additive)
- □ EDTA

12. _____ Prepare blood for testing at the local lab:
- □ CBC with differential and platelets
- □ BUN, Creatinine, ALT, AST
- □ Syphilis RPR
- □ HIV-1 serology

Tailor this item to reflect site-specific tube types and volumes.

13._____ Perform and document rectal exam using the *Final Clinic Visit Rectal Exam Checklist*. Record findings on the **Rectal Exam** CRF.

14. _____ Evaluate findings identified during rectal examination and medical and menstrual history review. Refer for or provide any clinically indicated treatment; document in chart notes and update **Concomitant Medications Log** CRF, if applicable.

15. _____ Schedule/remind the participant of the Follow-up Phone Assessment/Termination Visit and inform the participant of what to expect.

16._____ 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, contraceptive counseling, and/or condoms, if needed.

17. ____ Provide HIV test results in the context of post-test counseling, when available. [Before disclosing result(s) to participant, obtain independent review, verification, and sign-off of results(s)]. Provide referrals if needed/requested. Provide referrals if needed/requested. Provide treatment for RTIs/STIs if needed.

18._____ Provide study reimbursement.

Final Clinic Visit

PTID:	Visit Date:	Visit Code: 6.0

19. _____ Complete **AE Log** form(s), if required, based on interval medical/menstrual history, clinical exams/assessments, and lab tests when available.

20. _____ Complete the **Follow-up Visit/Phone Call** CRF.

21. _____ 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:

- ☐ LDMS Tracking Sheet
- ☐ Participant Reported Follow Up Medical and Menstrual History
- ☐ Physical Exam

22. _____ Fax all <u>required</u> DataFax forms to SCHARP:

- ☐ Anoscopy and Sigmoidoscopy Results
- ☐ Follow-up Visit/Phone Call
- ☐ Laboratory Results
- ☐ Rectal Exam
- ☐ Specimen Storage
- ☐ STI Laboratory Results
- ☐ Study Product Returns (for participants in the treatment arms only)

<u>*If applicable*</u>:

- ☐ Adverse Experience Log
- ☐ Concomitant Medication Log
- ☐ HIV Test Results
- ☐ Missed Visit
- ☐ Pregnancy Outcome
- ☐ Pregnancy Report and History

Final Clinic Visit Rectal Exam

PTID:	Visit Date:	Visit Code: 6.0

1. _____ Review chart notes and other relevant documentation.

2. _____ Explain the exam procedures to the participant and answer any participant questions.

3. _____ Affix a SCHARP-provided PTID labels to the specimen collection tubes at the time of collection. Record the PTID and write the specimen collection date in ink on the label.

4. _____ Position the participant in a lateral position on the left side. Drape the participant comfortably.

5. _____ Inspect the anus and surrounding area visually. Document abnormal findings on items # 1-1a of the **Rectal Exam** CRF and in chart notes.

6. _____ If clinically indicated, lubricant the anoscope with the study specified lubricant and insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

7. _____ If clinically indicated, collect the rectal swab for GC/CT testing by removing it from the plastic tube and inserting it through the anoscope placing in contact with the rectal wall. Gently turn the swab 360 degrees and remove. Place the rectal swab in the transport tube, break off shaft of swab and cap.

8. _____ Collect the rectal swab for **Microflora** by inserting the swab through the anoscope and place in contact with the rectal wall. Gently turn the swab 360 degrees gently and remove from rectum.

9. _____ Slowly remove the swab and place into a transport tube (labeled with a SCHARP-provided label), submerging the swab into the gel. Break off the shaft of the swab and cap.

10. _____ Collect the rectal sponge for **Cytokines** by inserting the sponge through the anoscope and place in contact with the rectum (approximately 9 cm in the rectum). *Note: The sponge should remain in place for five minutes*.

11. _____ Remove rectal sponge and place in a specimen collection tube (labeled with a SCHARP-provided label). Slowly remove anoscope.

Final Clinic Visit Rectal Exam

PTID:	Visit Date:	Visit Code: 6.0

12. _____ Perform a digital rectal examination by inserting a gloved finger, lubricated with study specified lubricant, into the anal canal and sweep around the internal anal circumference. Document abnormal findings on items #2-2a of the **Rectal Exam** CRF. Any unexpected discomfort should also be documented in chart notes and/or in the comments field of the **Rectal Exam** CRF.

13. _____ Position specimen pan provided in the Genova Diagnostic Calprotectin Kit onto available toilet.

14. _____ Prepare appropriate pre-packaged enema bottle for **Rectal Lavage** by applying a small amount of study specified lubricant to the tip of the enema bottle. Gently insert enema bottle into the rectum and and slowly dispell the fluid into the rectum.

Note: Instruct participant to hold the fluid in the rectum for approximately 3-5 minutes then expel it, including stool, into the specimen pan placed over the toilet.

15. _____ Transfer stool sample for **fecal calprotectin** with the flat wooden stick provided in the Genova Diagnostics-provided kit into the white top vial and prepare for transport.

16. ____ Transfer effluent for assessment of **epithelial sloughing** to a conical tube for initial processing and prepare per Section 12 of the SSP for shipment to the MTN Network Lab.

17. _____ Re-position the participant in a lateral position on the left side. Drape the participant comfortably.

18. _____ Use study provided lubricant to lubricate the tip of the sigmoidoscope. Insert the sigmiodoscope into the anal canal.

19. _____ Using the jumbo endoscopic foreceps, collect seven rectal biopsies at approximately 15 cm from the anal verge via flexible sigmoidoscopic biopsy. Remove sigmoidoscope following specimen collection.

20. _____ Use study provided lubricant to lubricate the anoscope. Insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

21. _____ Using the jumbo endoscopic foreceps, collect seven rectal biopsies at approximately 9 cm from the anal verge via **anoscopic** biopsy. Remove anoscope following specimen collection.

Final Clinic Visit Rectal Exam

PTID:	Visit Date:	Visit Code: 6.0

Note: Required biopsies are to be collected as follows:
_____1 biopsy at each location for Histology (15 cm and 9 cm)
_____2 biopsies at each location for Cytokine RT PCR (15 cm and 9 cm)
_____3 biopsies at each location for Mucosal T Cell Phenotyping (15 cm and 9 cm)
_____1 biopsy at each location for Mucosal Gene Expression Array (15 cm and 9 cm)

22. _____ Obtain vital signs and document in chart notes. Evaluate any abnormal findings.

23. _____ Document exam findings on the **Anoscopy and Sigmoidoscopy Results** CRF. Document specimen collection and storage on the **Specimen Storage** CRF and the **LDMS Specimen Tracking Sheet** (non-DataFax) CRF.

Follow-Up Phone Assessment/Termination Visit

PTID:	Visit Date:	Visit Code: 7.0

1. _____ Confirm the participant's identity and verify PTID per site SOPs.

2. _____ Review chart notes and other relevant documentation from previous visit(s).

3. _____ Review elements of informed consent as needed. Explain the content and purpose for the follow up phone assessment.

4. _____ Inquire about any AEs the participant may have experienced as a result of study product or procedures performed during the Final Clinic Visit.

5. _____ Refer for follow-up care as needed. Document follow-up in chart notes. If required based on all available information, complete **AE Log** CRF.

6. _____ 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, contraceptive counseling, and/or condoms, if needed.

7. _____ Complete **Follow-up Visit/Phone Call** CRF and **Termination** CRF

8. _____ Document the visit in a signed and dated chart note.

9. _____ Complete and review case report forms and participant chart contents for the visit.

10. _____ Fax all <u>required</u> DataFax forms to SCHARP:
    - ☐ Follow-up Visit/Phone Call
    - ☐ End of Study Inventory
    - ☐ Termination

    If applicable:
    - ☐ AE Log Form
    - ☐ Missed Visit

Additional Comments:

_____
_____
_____
_____
_____

Interim Visit

PTID:	Visit Date:	Visit Code:

1. _____ Confirm the participant's identity and verify PTID per site SOPs.

2. _____ Review/update locator information.

3. _____ Review chart notes and other relevant documentation from previous visit(s). Provide test results from previous visit(s), if applicable.

4. _____ Review elements of informed consent as needed. Explain the content and sequence of procedures for today's visit

5._____ Collect 15-60 mL urine and:

- 5a. _____ Aliquot approximately 5-10 mL for qualitative pregnancy ***(for females of childbearing potential only)***.
- 5b. _____ Complete testing logs and record result on the **Interim Visit** CRF.
- 5c. _____ If clinically indicated, complete dipstick urinalysis and record results for protein, glucose, nitrites, and leukocytes according to local SOP and on **Laboratory Results** CRF. If dipstick urinalysis is positive for leukocytes or nitrites, provide treatment and/or additional UTI work-up per site. Document treatment and/or additional work-up in chart notes. Update Concomitant Medications Log if necessary.
- 5d. _____ If clinically indicated, prepare remaining urine for gonorrhea and chlamydia NAAT. Record results on **STI Laboratory Results** CRF, when available.

If the participant is pregnant, modify remaining study visit procedures per protocol section 7.8.2. If the participant is pregnant and is randomized to gel arm:

- 5e. _____ Complete a **Pregnancy Report and History** CRF and a **Product Hold/Discontinuation Log** CRF

6._____ Perform interval medical/menstrual history, record findings on the **Participant Reported Follow-up Medical and Menstrual History** (non-DataFax) CRF. Review and update the **Concomitant Medications Log** (including family planning methods) as necessary.

7. _____ If clinically indicated, perform physical exam as per protocol section 7.11 and record findings on the **Physical Exam** (non-DataFax) CRF.

8. ____ If clinically indicated, perform and document rectal exam using the *Interim Visit Rectal Exam Checklist*. Record findings on the **Rectal Exam** CRF.

Interim Visit

PTID:	Visit Date:	Visit Code:

9. _____ Evaluate findings identified during rectal and physical examinations and medical and menstrual history review. Refer for or provide any clinically indicated treatment; document in chart notes and update **Concomitant Medications Log** CRF, if applicable.

10. _____ If HIV testing is clinically indicated, provide HIV pre-test counseling.

11._____ If clinically indicated, collect blood:

- □ Plain tube (no additive)
- □ EDTA

12._____ Prepare blood for testing at the local lab:

- □ HIV-1 serology (if indicated)
- □ Syphilis RPR (if indicated)
- □ CBC with differential and platelets (if indicated)
- □ BUN, Creatinine, ALT, AST (if indicated)

Tailor this item to reflect site-specific tube types and volumes.

13._____ **ASSESS ELIGIBILITY TO CONTINUE PRODUCT USE BASED ON INTERVAL MEDICAL/MENSTRUAL HISTORY AND RECTAL EXAM FINDINGS, IF APPLICABLE**

NOT ELIGIBLE (Gel Participants Only): Refer to Protocol Section 9.4 and the SSP Manual, Section 10, for guidelines on discontinuing study product. Contact PSRT if there are any questions.

13a. _____ If product use is discontinued at this visit, document the rationale in chart notes and/or on other applicable source documents. Complete the **Product Hold/Discontinuation Log** and a **Study Gel Request Slip** to inform the site's pharmacist of the product discontinuation.

13b. _____ Deliver the white copy of the completed Study Gel Request Slip to the pharmacy; retain the yellow copy in the participant's study notebook.

14. ____ **Gel Participants Only:** If study product is resupplied at this visit, complete a **Study Gel Request Slip**. Document the rationale in chart notes and/or on other applicable source documents. Contact the PSRT if there are any questions about study product or clinical management. If product use is discontinued, collect used and unused study product. Document product collection in the chart notes and on the **Interim Visit** CRF. If participant did not bring the unused product at this visit, make arrangements to collect the product.

Interim Visit

PTID:	Visit Date:	Visit Code:

15. _____ Provide and explain available exam and lab test results. Provide post-test counseling and appropriate referrals, if applicable. Provide HIV/STI risk reduction and condom counseling. Provide study-specific male condoms and lubricants. Provide referrals if needed/requested.

16._____ Complete/update **Adverse Experience Log** CRF, if required, based on interval medical/menstrual history, clinical exams/assessments, and lab tests when available.

17._____ Reinforce site contact information and instructions to contact the site to report symptoms — especially rectal symptoms — and/or to request for additional information, HIV/STI counseling, and/or condoms, if needed, prior to the next visit.

18. _____ Remind/schedule the participant of their next scheduled visit, if applicable.

19. _____ Complete **Interim Visit** CRF.

20. ____ Document the interim visit in a signed and dated chart note. Complete and review all participant chart contents and case report forms for the visit, including the following non-DataFax forms:

- ☐ Participant-reported Follow-up Medical and Menstrual History
- ☐ LDMS Specimen Tracking Sheet, *if applicable*
- ☐ Physical Exam, *if applicable*

21. _____ Fax all <u>required</u> Data Fax forms to SCHARP:

- ☐ Interim Visit

<u>*If applicable*</u>:

- ☐ Adverse Experience Log
- ☐ Concomitant Medication Log
- ☐ HIV Test Results
- ☐ Laboratory Results
- ☐ Pregnancy Outcome
- ☐ Pregnancy Report and History
- ☐ Product Hold/Discontinuation Log
- ☐ Rectal Exam
- ☐ STI Laboratory Results

Interim Visit Rectal Exam

PTID:	Visit Date:	Visit Code:

Mark "Not applicable or N/A" next to all procedures that are not clinically indicated for the visit.

1. _____ Review chart notes and other relevant documentation.

2. _____ Explain the exam procedures to the participant and answer any participant questions.

3. _____ Affix a SCHARP-provided PTID labels to the specimen collection tubes at the time of collection. Record the PTID and write the specimen collection date in ink on the label.

4. _____ Position the participant in a lateral position on the left side. Drape the participant comfortably.

5. _____ Inspect the anus and surrounding area visually. Document abnormal findings on items # 1-1a of the **Rectal Exam** CRF and in chart notes.

6. _____ Lubricate the anoscope with the study specified lubricant and insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

7. _____ Collect the rectal swab for GC/CT testing by removing it from the plastic tube and inserting it through the anoscope placing in contact with the rectal wall. Gently turn the swab 360 degrees and remove. Place the rectal swab in the transport tube, break off shaft of swab and cap. Slowly remove anoscope.

8. _____ Perform a digital rectal examination by inserting a gloved finger, lubricated with study specified lubricant, into the anal canal and sweep around the internal anal circumference. Document abnormal findings on items #2-2a of the **Rectal Exam** CRF. Any unexpected discomfort should also be documented in chart notes and/or in the comments field of the **Rectal Exam** CRF.

9. _____ Use study provided lubricant to lubricate the tip of the sigmoidoscope. Insert the sigmiodoscope into the anal canal.

10. _____ Using the jumbo endoscopic foreceps, collect seven rectal biopsies at approximately 15 cm from the anal verge via flexible sigmoidoscopic biopsy. Remove sigmoidoscope following specimen collection.

11. _____ Use study provided lubricant to lubricate the anoscope. Insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

Interim Visit Rectal Exam

PTID:	Visit Date:	Visit Code:

Mark "Not applicable or N/A" next to all procedures that are not clinically indicated for the visit.

12. _____ Using the jumbo endoscopic foreceps, collect seven rectal biopsies at approximately 9 cm from the anal verge via **anoscopic** biopsy. Remove anoscope following specimen collection.

Note: Required biopsies are to be collected as follows:
_____1 biopsy at each location for Histology (15 cm and 9 cm)
_____2 biopsies at each location for Cytokine RT PCR (15 cm and 9 cm)
_____3 biopsies at each location for Mucosal T Cell Phenotyping (15 cm and 9 cm)
_____1 biopsy at each location for Mucosal Gene Expression Array (15 cm and 9 cm)

13. _____ Obtain vital signs and document in chart notes. Evaluate any abnormal findings.

14. _____ Document exam findings on the **Anoscopy and Sigmoidoscopy Results** CRF. Document specimen collection and storage on the **Specimen Storage** CRF and the **LDMS Specimen Tracking Sheet** (non-DataFax) CRF.

Early Termination Visit

PTID:	Visit Date:	Visit Code:

1. _____ Confirm the participant's identity and verify PTID per site SOPs.

2. _____ Review/update locator information.

3. _____ Review chart notes and other relevant documentation from previous visit(s). Provide test results from previous visit(s), if applicable.

4. _____ Review elements of informed consent as needed. Explain the content and sequence of procedures for today's visit. Determine visit code for this visit (regular or interim) based on participant's completed visits and visit window calendar.

5._____ Collect 15-60 mL urine and:

- 5a. _____ Aliquot approximately 5-10 mL for qualitative pregnancy ***(for females of childbearing potential only)*** and dipstick urinalysis tests.
- 5b. _____ Complete testing logs and record result on the **Follow Up Visit/Phone Call** CRF or **Interim Visit** CRF (depending on visit code assigned to the visit).
- 5c. _____ Complete dipstick urinalysis and record results for protein, glucose, nitrites, and leukocytes according to local SOP and on **Laboratory Results** CRF. Document treatment and/or additional work-up in chart notes. Update **Concomitant Medications Log** if necessary.
- 5c. _____ If clinically indicated, prepare remaining urine for gonorrhea and chlamydia NAAT. Record results on **STI Laboratory Results** CRF, when available.

If the participant is pregnant, modify remaining study visit procedures per protocol section 7.8.2. If the participant is pregnant and is randomized to gel arm:

- 5e. _____ Complete a **Pregnancy Report and History** CRF.

6. _____ ***Gel participants Only*****:** If applicable, collect used and unused study product. Document product collection in the chart notes. If participant did not bring the unused product at this visit, make arrangements to collect the product. Complete **Study Product Returns** CRF. If participant is terminating prior to the Treatment 1 or Treatment 2 Visit, complete a MTN-007 Study Product Request Slip for the pharmacy to document permanent discontinuation of study product.

Early Termination Visit

PTID:	Visit Date:	Visit Code:

7. _____ Perform interval medical/menstrual history, recording information on the **Participant Reported Follow-up Medical and Menstrual History** form. Review and update the **Concomitant Medications Log** (including family planning methods) as necessary.

8. _____ Conduct physical exam as per protocol section 7.11 and record findings on the **Physical Exam** (non-DataFax) CRF.

9. ____ ***Gel Participants Only***: Administer Product Acceptability Questionnaire.

10. ____ Provide HIV pre-test, HIV/STI risk reduction and condom counseling. Provide study-specific male condoms. Provide referrals if needed/requested.

11._____ Collect blood:
- □ Plain tube (no additive)
- □ EDTA

12. _____ Prepare blood for testing at the local lab:
- □ CBC with differential and platelets
- □ BUN, Creatinine, ALT, AST
- □ Syphilis RPR
- □ HIV-1 serology

Tailor this item to reflect site-specific tube types and volumes.

13._____ Perform and document rectal exam using the *Early Termination Visit Rectal Exam Checklist*. Record findings on the **Rectal Exam** CRF.

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14. _____ Evaluate findings identified during rectal and physical examinations and medical and menstrual history review. Refer for or provide any clinically indicated treatment; document in chart notes and update **Concomitant Medications Log** CRF, if applicable.

15. ____ If applicable, schedule Follow-up Phone Assessment and inform the participant of what to expect.

16. ____ Provide HIV test results in the context of post-test counseling when available. [Before disclosing result(s) to participant, obtain independent review, verification, and sign-off of results(s)]. Provide referrals if needed/requested. Provide referrals if needed/requested. Provide treatment for RTIs/STIs if needed.

17._____ Provide study reimbursement.

Early Termination Visit

PTID:	Visit Date:	Visit Code:

18. _____ Complete **AE Log** form(s), if required, based on interval medical/menstrual history, clinical exams/assessments, and lab tests when available.

19. _____ Complete the remainder **Follow-up Visit/Phone Call** or **Interim Visit** CRF, as applicable.

20. _____ Complete the **Termination** CRF and **End of Study Inventory** CRF.

21. _____ 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:

- ☐ LDMS Tracking Sheet (if rectal specimens for storage were collected)
- ☐ Participant Reported Follow Up Medical and Menstrual History
- ☐ Physical Exam

22. _____ Fax all <u>required</u> DataFax forms to SCHARP:

- ☐ Follow-up Visit/Phone Call or Interim Visit
- ☐ Anoscopy and Sigmoidoscopy Results, if applicable
- ☐ Specimen Storage, if applicable
- ☐ Laboratory Results
- ☐ Rectal Exam
- ☐ STI Laboratory Results
- ☐ Study Product Returns (for participants in the treatment arms only and if applicable)
- ☐ End of Study Inventory
- ☐ Termination

<u>*If applicable*</u>:

- ☐ Adverse Experience Log
- ☐ Concomitant Medication Log
- ☐ HIV Test Results
- ☐ Missed Visit
- ☐ Pregnancy Outcome
- ☐ Pregnancy Report and History

Early Termination Visit Rectal Exam

PTID:	Visit Date:	Visit Code:

Mark "Not applicable or N/A" next to all procedures that are not clinically indicated for the visit.

1. ____ Review chart notes and other relevant documentation.

2._____Explain the exam procedures to the participant and answer any participant questions.

3._____Affix a SCHARP-provided PTID labels to the specimen collection tubes at the time of collection. Record the PTID and write the specimen collection date in ink on the label.

4._____Position the participant in a lateral position on the left side. Drape the participant comfortably.

5._____Inspect the anus and surrounding area visually. Document abnormal findings on items # 1-1a of the **Rectal Exam** CRF and in chart notes.

6._____If clinically indicated, lubricate the anoscope with the study specified lubricant and insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

7._____If clinically indicated, collect the rectal swab for GC/CT testing by removing it from the plastic tube and inserting it through the anoscope placing in contact with the rectal wall. Gently turn the swab 360 degrees and remove. Place the rectal swab in the transport tube, break off shaft of swab and cap. Remove anoscope following specimen collection.

8._____Perform a digital rectal examination by inserting a gloved finger, lubricated with study specified lubricant, into the anal canal and sweep around the internal anal circumference. Document abnormal findings on items #2-2a of the **Rectal Exam** CRF. Any unexpected discomfort should also be documented in chart notes and/or in the comments field of the **Rectal Exam** CRF.

9. ____If clinically indicated, use study provided lubricant to lubricate the tip of the sigmoidoscope. Insert the sigmiodoscope into the anal canal.

10.____Using the jumbo endoscopic foreceps, collect seven rectal biopsies at approximately 15 cm from the anal verge via flexible sigmoidoscopic biopsy. Remove sigmoidoscope following specimen collection.

Early Termination Visit Rectal Exam

PTID:	Visit Date:	Visit Code:

Mark "Not applicable or N/A" next to all procedures that are not clinically indicated for the visit.

11. ___If clinically indicated, use study specified lubricant to lubricate the anoscope. Insert the anoscope into the anal canal until the anoscope 'wings' touch the anal verge. Remove the obturator.

12. ___Using the jumbo endoscopic forceps, collect seven rectal biopsies at approximately 9 cm from the anal verge via **anoscopic** biopsy. Remove anoscope following specimen collection.

    Note: Required biopsies are to be collected as follows:
    _____1 biopsy at each location for Histology (15 cm and 9 cm)
    _____2 biopsies at each location for Cytokine RT PCR (15 cm and 9 cm)
    _____3 biopsies at each location for Mucosal T Cell Phenotyping (15 cm and 9 cm)
    _____1 biopsy at each location for Mucosal Gene Expression Array (15 cm and 9 cm)

13._____Obtain vital signs and document in chart notes. Evaluate any abnormal findings.

14.____Document exam findings on the **Anoscopy and Sigmoidoscopy Results** CRF. Document specimen collection and storage on the **Specimen Storage** CRF and the **LDMS Specimen Tracking Sheet** (non-DataFax) CRF.

Section 8. Participant Retention

This section presents information related to definitions, requirements and procedures for participant retention in MTN-007.

8.1 Retention Definitions

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. For MTN-007, two retention measures are planned: one during the study and one at the end of the study. Additional retention measures may be defined and used during the study if desired by the Protocol Chair and/or Protocol Statisticians.

- During the study, retention for scheduled (required) follow-up visits will be defined based on whether participants complete some part of the required scheduled visits within the allowable visit window. Participants who complete all or part of their scheduled visits within the allowable visit window will be considered "retained" for those visits.

- At the end of the study, retention will be defined based on whether participants complete the Final Phone Assessment Visit/Termination Visit. Although every effort must be made to complete each participant's study Final Clinic Visit and subsequent Follow-up Phone Assessment Visit/Termination Visit within the allowable visit window, these visits will be allowed to take place through the study end date. Participants who complete this visit will be considered retained.

As indicated above, participants who do not complete a particular scheduled visit within the allowable 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 that was completed. 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.

8.2 Retention Requirements

Each study site will target retention of at least 95 percent of enrolled study participants for each scheduled follow-up visit. The purpose of the 95 percent retention target is to ensure the accuracy of study results by minimizing bias that can be caused by missing data. Low retention rates can have serious impacts on the accuracy of the study results because we cannot know if participants who do not return for scheduled study visits used the product, liked the product or had ill effect from the use of the product.

8.3 Retention SOPs

Site staff are responsible for establishing a standard operating procedure (SOP) for participant retention to meet the goal of 95 percent. The SOP should minimally contain the following elements:

- Site-specific retention goals
- Methods for tracking actual retention versus retention goals
- Procedures for collecting and updating participant locator information
- Site-specific definition of "adequate" locator information (for purposes of determining participant eligibility)
- Visit reminder methods and time frames
- Methods and timeframes for identifying when a visit has been missed
- Planned retention methods, including what outreach/locator efforts are taken with 24 hours, 1-3 days, 1 week and 2 weeks 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 elsewhere)
- QC/QA procedures related to the above (if not elsewhere)

8.4 Obtaining and Updating Locator Information

Successful retention begins with collection of exhaustive locator information from each study participant. All study participants will be asked to provide locator information during the study screening process and to continually review/update this information during follow-up. Provision of "adequate" locator information during screening is a study eligibility requirement and each site must specify its definition of adequate locator information in its retention SOP.

Each site is encouraged to develop a locator form to maximize contact effectiveness and participant retention. Sites also may wish to consider having outreach workers accompany participants to their homes or other community based locations to verify or further clarify their locator details. Practical locator items include:

- Participant's full name, alias, and/or nickname; government issued identification number; home address; home phone number; mobile phone number; work address; work phone number; fax number; e-mail address; daytime and nighttime locations, meeting places and hangouts.
- Walking/driving/public transport directions and/or other contact information for stable community contacts (i.e., family members and friends) who typically know the whereabouts of the participant.
- Note: Although contact information for a participant's current primary partner will likely be useful, contact information for other contacts also should 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.

- 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 locator information, study participants must be informed that their locator 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 locator sources are contacted. Arrangements agreed upon with the participant should be documented on the locator form.

Study staff should view every contact with the participant as an opportunity to update the participant's locator information. When updating locator information, actively review each item on the locator form to determine whether the information is still current (rather than simply asking "Has any of your information changed since the last visit?"). Staff should also probe for additional information that the participant was not able or willing to provide at previous visits.

8.5 Retention Tips

Some general strategies for maximizing participant retention are as follows:

- Thoroughly explain of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit. When participants complete scheduled visits, acknowledge and comment on their commitment, time and effort devoted to the study.
- Thoroughly explain of the importance of completing all study visits to the overall success of the study.
- Collect detailed locator information at the study screening visit and active review and updating of this information at each subsequent visit.
- Use mapping techniques to establish the location of participant residences and other locator venues.
- Mobilize trained outreach workers or "tracers" to complete in-person contact with participants at their homes and/or community locations
- 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
- 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.
- Use the visit calendar created for the participant to identify when the participant's 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/Baseline Evaluation 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.
- For participants who demonstrate a pattern of late or missed appointments, schedule follow-up visits for the beginning of the allowable visit window to allow maximum time for re-contract and re-scheduling, if needed.

- Play close attention to the allowable 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 locator 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 information collected on the participant's locator form. Even if a locator form is not useful/successful on one occasion, try it again later.
- 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 locator information sources, such as phone and postal directories and other public registries.
- Post outreach workers at other local service organizations utilized 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 he/she wishes to discontinue participation in the study, explain that he/she is always welcome to come back if he/she wishes.

Section 9. Study Product Considerations for Non-Pharmacy Staff

This section provides information and instructions for non-pharmacy staff related to the ordering, transport, delivery and administration of MTN-007 study product for study participants. Associated instructions for pharmacy staff are provided in the *MTN-007 Pharmacy Policies and Procedures Manual*, which will be made available to each site Pharmacist of Record (PoR) by the MTN CORE Pharmacist. Please also refer to related information in Sections 4 and 6 of this manual.

9.1 Responsibilities and Obligations with Regard to Blinding

MTN-007 Investigators of Record (IoRs), and by delegation all MTN-007 study staff, are responsible for maintaining the integrity of the study's blinded design. Although the assignment to "gel" or "no gel" cannot be blinded, the identity of the specific gel product to which each participant is assigned is double-blinded. This means that neither study participants nor study staff — including all members of the Protocol Team and site pharmacy staff — will be provided information on the identity of the specific gel to which each participant has been assigned.

Study documentation maintained by clinic staff (such as the documents contained inside the Clinic Randomization Envelopes) will identify whether participants have been assigned to "gel" or "no gel." Study documentation maintained by pharmacy staff (such as the documents contained inside the Pharmacy Randomization Envelopes) will include coded information indicating the specific gel product to which participants have been assigned. Access to study pharmacy facilities, and all study product supplies and documentation stored in these facilities, is limited to site pharmacy staff only.

Additional operational requirements to preserve blinding are as follows:

- Clinic staff should respond to participant questions about how to store product supplies, and how to insert gel. Sample gel applicators should be stocked at all clinic locations for educational and counseling purposes. Actual study products may not be used for educational and counseling purposes.

- Clinic staff may not unwrap applicators or handle individual applicators.

- At Treatment Visit 2, clinic staff will provide each participant with 2 transparent bags to collect used and unused applicators. Participants will be instructed to collect the used applicators in the bag labeled "USED" and the unused (wrapped or unwrapped) applicators should be placed in the bag labeled "UNUSED". Participants will be instructed to bring both bags, all used and unused study product to their Final Clinic Visit. Clinic staff will collect the bags of used and unused study product and record the count in the participant's study record as well as the Study Product Returns case report form. The applicators should remain in the bags and should not be handled directly.

- After counting the returned applicators, all bags of **used** applicators should be placed in a designated biohazard container in the clinic in accordance with the guidelines of the institution. When the study is completed or the container is full, the biohazard container should be destroyed in accordance with the policy of the institution. All bags of **unused** applicators should be sent to the pharmacy and placed in quarantine and returned at completion of the study (see *MTN-007 Pharmacy Policies and Procedures Manual*).

- In the event that a participant reports damage or other issues or problems with his/her study product — (not including signs, symptoms, or adverse events associated with product use) — clinic staff should refer the participant to the PoR to further discuss and evaluate the study product concerns. Clinic staff should not inspect study product in any way and under no circumstances should clinic staff dispense gel from any applicators.

- If the participant's study product supplies have been damaged, the PoR will collect the damaged supplies from the participant. 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 Sponsors of the occurrence.

- If the PoR determines that the participant requires additional instruction on how to insert applicators, the PoR will refer the participant back to clinic staff for refresher education and counseling.

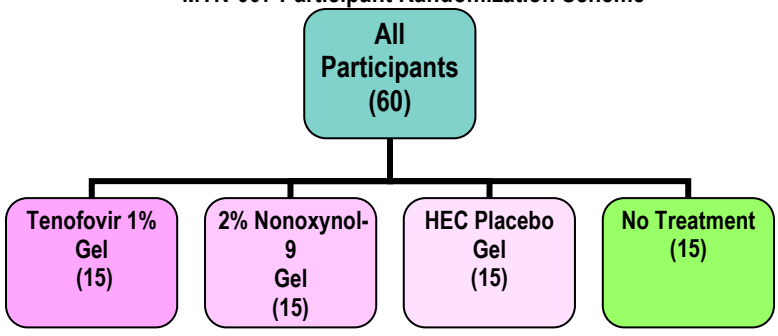
- The PoR will document his/her interactions with participants, and subsequent action taken, in signed and dated notes that are retained in participant-specific pharmacy files. The PoR will forward copies of written documentation that contains no random assignment information to clinic staff to ensure timely clinic staff awareness of the resolution of participant reports. If circumstances require the PoR to dispense additional study product supplies to a participant (to replace lost or damaged product, for example), the PoR will collaborate with clinic staff to obtain a newly completed MTN-007 Study Product Request Slip ordering the necessary additional study product supplies.

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 his/her study product, the IoR may discontinue product use by the participant; however, knowledge of the specific gel to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an IoR feels that product-specific information is necessary to protect participant safety, he/she should notify the MTN-007 Protocol Safety Review Team (PSRT).

9.2 Study Product Regimens

As shown in Figure 9-1, study participants will be randomly assigned in equal numbers to one of three blinded study regimens or to no treatment (four study group's total).

Figure 9-1
MTN-007 Participant Randomization Scheme



9.3 Gel Use Instructions

At the Treatment 1 Visit, participants, under observation of the site clinician, will insert the contents of one study applicator. Clinic staff will instruct the participant to use a small amount of the Pre′ Vaginal Lubricant on the outside of the applicator. The clinic will maintain a supply of the Pre′ Vaginal Lubricant for use during observed administrations. At the Treatment 2 Visit, participants will be instructed to insert the entire contents of one applicator into the rectum, once daily throughout the 7-day period. Clinic staff will provide the participants with 7 packets of Pre′ Vaginal Lubricant.

Rectal administration of the study gel should occur before bedtime, or the longest period of rest. If a participant misses a dose, the participant must insert rectally the missed dose as soon as possible, unless the next dose is estimated to be due within six hours. If the next dose is estimated to be due within six hours, the missed dose must be skipped. The next dose will be inserted rectally as originally scheduled. Participants will be instructed to insert the gel as close to the same time each day as possible.

Detailed instructions for application of gel are listed in Appendix 9-1.

9.4 Dispensing Study Products during On-Site Visits

Please refer to Sections 4 and 6 of this manual for further information on procedures for participant randomization, and initial ordering and dispensation of study products for enrolled participants. Instructions for completing MTN-007 Prescriptions and MTN-007 Study Product Request Slips are provided in those sections.

At the Treatment 1 Visit, upon receipt of a completed and signed MTN-007 Prescription, a single prefilled applicator of gel will be dispensed by the pharmacy for use by participants randomized to "gel" per instructions in the *MTN-007 Pharmacy Policies and Procedures Manual*. Following at least a 7-day washout period, at the Treatment 2 Visit, participants randomized to "gel" will receive 8 pre-filled applicators of gel from the pharmacy upon receipt of a completed and signed MTN-007 Prescription. Although participants should only require 7 applicators, they will receive one extra should one of the applicators not be usable for any reason.

Upon receipt of a completed and signed MTN-007 Study Product Request Slip, pharmacy staff will dispense additional study product for participants, as needed, per instructions in the *MTN-007 Pharmacy Policies and Procedures Manual*.

The PoR will label the applicators in accordance with state and site requirements. Labeling will also include the PTID of the participant for whom the products are prepared.

In the remainder of this section, study products prepared by pharmacy staff for dispensation to participants are referred to as "participant-specific study product."

Participant-specific study product may be dispensed to participants in one of two ways:

- From the pharmacy directly to the participant
- From the pharmacy to an authorized clinic staff member who will then deliver the applicator(s) to the participant

The *MTN-007 Pharmacy Policies and Procedures Manual* will outline the randomization, dispensing and product re-supply process. If a site chooses to use a process other than those outlined in the manual an SOP must be written. 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 dispensing method is provided in Sections 9.4.1 and 9.4.2 below.

9.4.1 Dispensing from the Pharmacy Directly to Participants

At sites choosing to dispense participant-specific study product directly from the pharmacy to participants, prescriptions and product 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 correctly completed and signed prescription or product request slip, the PoR will prepare the number of gel applicators entered on the prescription or request slip.

9.4.2 Dispensing from the Pharmacy to Clinic Staff

At sites choosing to dispense participant-specific study product to clinic staff who will then deliver the product to participants, prescriptions and product request slips are expected to be delivered to the pharmacy by clinic staff or a runner. Upon receipt of a correctly completed and signed prescription or product request slip, the PoR will prepare the number of gel applicators entered on the prescription or request slip.

The MTN-007 Record of Receipt of Participant-Specific Study Product (see Appendix 9-2) or other site specific form must be used to document dispensing of participant-specific study product to clinic staff. Pharmacy staff will complete the top section (site name, site number, clinic name) and the first four columns on the Record of Receipt. When receiving product supplies from the pharmacy, clinic staff will verify the PTIDs, confirm the number of applicators 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 applicators dispensed into their custody and ensuring that the applicators are delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of the applicator to designated participants in the participants' chart notes. Delivery may be documented in chart notes or on other source documents designated for this purpose. In the event that all gel applicators dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the applicators to the pharmacy as soon as the participant's visit is completed.

9.5 Study Product Returns

Participants will be instructed to bring all used and unused study product to the Final Clinic Visit as described in Section 9.1 of this manual.

Clinic staff will provide participants with plastic bag containers in which to store their used and unused applicators. Clinic staff should also install biowaste receptacles for use once the returned product is documented. Bags of used applicators should be collected and disposed of in the biowaste container in accordance with applicable biowaste requirements. Bags of unused applicators should be sent to the pharmacy and placed in quarantine.

9.6 Study Product Retrieval

Because participants are instructed to bring all used and unused study product to the Final Clinic Visit, the need for product retrieval is expected to be rare. When product retrieval is required, retrieval may occur either by the participant returning the product to study staff or by study staff conducting outreach to retrieve the product from the participant (e.g., at home).

If a participant does not return remaining product (in most cases this will only be 1 unused applicator and 7 used applicators returned) on the day of the Final Clinic Visit, arrangements must be made to collect the remaining supplies as soon as possible. If the remaining study product is not retrieved within five working days after the Final Clinic Visit, the PSRT must be informed and the PoR must inform the MTN Pharmacist.

Appendix 9-1
Gel Use Instructions

Preparing the Applicator:

- Tear open the wrapper and remove the applicator (capped barrel and plunger), which is already pre-filled with gel.
- Gently place the small end of the plunger in the hole at the back end of the barrel (opposite blue cap).
- Remove the blue cap from the end of the barrel.
- Apply a dime-size amount of the Pre´ Vaginal Lubricant provided by the study staff to the outside of the barrel of the applicator. Do not insert the applicator without lubricant, as the dry applicator may cause discomfort.

Inserting the Applicator:

- Find the position that feels most comfortable. Many people already have a position they prefer (kneeling, squatting, etc.). If you do not have a preferred position, we recommend that you lie on your left side or on your back.
- Hold the applicator with your thumb and middle finger about half-way along the barrel
- Insert the applicator tip between your legs and into the anus slowly and gently.
- Once the tip is partially into the rectum, gently slide the applicator until you feel your fingers touch your body. Do not insert the applicator all the way. You only need to insert the applicator 2-3 inches (about ½ way).
- Do not force the applicator into the rectum as this can cause injury. Stop if you meet resistance.
- While holding the applicator in place, push the plunger until it stops to release the gel.
- Withdraw the applicator from your anus.

Alternative Positions:

If you are lying on your left side:

a) The right leg should be bent up toward the chest.
b) Use your right hand to guide in the applicator tip by reaching around behind you.
c) Insert the applicator tip between your legs and into the anus slowly and gently.
d) Once the tip is partially into the rectum, tilt the applicator slightly toward your belly button. It should then advance easily.

Left Side
Lie on your left side. The right leg should be bent up toward the chest.

If you are lying on your back:

a) Lie on your back with your right knee bent. This should allow good access to your rectum from below.
b) Insert the applicator tip between your legs and into the anus slowly and gently.

Follow Up Instructions:

- Do not wash or wipe off the applicator
- Place the used applicator in the re-sealable bag labeled "USED APPLICATORS" provided to you by study staff.
- Place and any UNUSED applicators in the second bag provided to you by study staff labeled "UNUSED APPLICATORS"
- Bring both of the bags (USED applicators and UNUSED applicators) to the Final Clinic Visit

Helpful Hints:

- Insertion may be easier if you bear down, as if having a bowel movement. This helps relax the muscles around the anus.

Sometimes a slight rolling/twisting of the wrist can make insertion of the tip easier.

Appendix 9-2

RECORD RECIEPTS OF PARTICIPANT-SPECIFIC STUDY PRODUCT

Site Number:	**Site/ Clinic Name:**

PHARMACY STAFF				**CLINIC STAFF/RUNNER**			
Date Dispensed by Pharmacy dd-mm-yy	PTID	Number of Study Gel applicators Dispensed by Pharmacy	RPh Initials	PTID (Verify PTID)	Date and Time Received by Clinic Staff/ Runner dd-mm-yy 00:00 AM/PM	Clinic Staff /Runner Initials	Comments

Instructions: Complete one row each time a carton is 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.

Appendix 9-3
Frequently Asked Product Use Questions

9-2.1 What is the best position to insert the study gel?
Find the position that feels most comfortable. Many people already have a position they prefer (kneeling, squatting, etc.). If you do not have a preferred position, we recommend that you lie on your left side or on your back.

9-2.2: What should I do if it hurts when I use the applicator to insert the study gel?
Inserting the study gel should not be painful. If you have pain when inserting the study gel, try another position. If you still have pain in the new position, perhaps you need to change the angle of the applicator. The applicator should be slightly lubricated with the lubricant provided by the clinic staff. If you still feel pain on insertion, please contact the study clinic.

9-2.3: Where does the study gel go to after I put it inside?
The study gel stays in the rectum. Some study gel will likely come out of the rectum over time.

9-2.4: Can the applicator get lost inside me?
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. Once completed, remove the entire applicator and discard.

9-2.5: What should I do if I have trouble inserting the study gel with the applicator?
The applicators should be easy to use. The applicator should be slightly lubricated with the lubricant provided by the clinic staff. 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 study gel, which might make it easier.

9-2.6: What should I do if I think there is something wrong with an applicator?
If there seems to be something wrong with an applicator (for example, you find it difficult to push the study gel out of the applicator, or if study 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 bring it to the study pharmacy 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.

9-2.7: What happens if I press the plunger too early and most of the study gel comes out on my outside?
If most of the study gel comes out on your outside, Dispose of that applicator and use a new applicator to insert another dose of study gel. If this occurs with more than one applicator , 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 .

9-2.7: How do I store the study gel?
Store the study gel in a cool, dry place at room temperature and not in the sun.

9-2.8: What happens if the applicators get wet before I use them?

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.

9-2.9: What should I do if the wrapper is already open when I want to use the study gel?

You should only use applicators with sealed wrappers, so you should always open the wrapper right before inserting the study 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 bring it to the study pharmacy at your next study visit.

9-2.10: What should I do if I forget to insert the study gel one day?

You must insert rectally the missed dose as soon as possible, unless the next dose is estimated to be due within six hours. If the next dose is estimated to be due within six hours, the missed dose must be skipped. The next dose will be inserted rectally as originally scheduled.

9-2.11: What should I do if I have a reaction to the study gel (e.g., unusual itching, stinging)?

Contact the study clinic and ask their advice. They might ask you to go to the clinic to be assessed and receive treatment if needed.

9-2.12: What should I do if I think I am pregnant?

Contact the study clinic immediately. The clinic staff will give you a pregnancy test to find out if you are pregnant or not.

9-2.13: Can I use the study gel before oral sex (i.e., no intercourse)?

The gel may be inserted prior to oral (penile or vaginal) sex.

9-2.14: Can I have sex after inserting study gel?

You need to abstain from RAI for the duration of study participation. Vaginal and insertive anal intercourse is permitted with the use of study provided condoms.

9-2.15: Does it matter what brand condoms we use?

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. If a condom other than the condoms given to you by the study clinic staff is used, inform the study clinic staff of the change. Condoms are the only known way to protect against HIV and other sexually transmitted diseases (STIs), 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.

9-2.16: What should I do if the study gel leaks out?

It is likely that some study gel will leak out. This is normal and you don't need to do anything about it. You should always insert 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 study gel, if you find that a small amount leaks out.

9-2.17: Can I use herbs or other substances for tight or dry sex while I am using the study gel?

Participants should refrain from any practices which include rectal insertion of ay product including those used during sexual intercourse (sex toys).

9-2.18: Does it matter if I do not insert the study gel at the same time every day (at bedtime or longest period of rest)?

Ideally, you should insert the study gel at bedtime or longest period of rest, to prevent the study gel from leaking out when you are standing or being active.

9-2.19: Can my partner insert the study gel for me?

It is preferable that you insert the study 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 study gel for you than to not use the study gel at all.

9-2.20: Will I have access to the study gel if it is shown to be effective?

If the study gel is shown to be safe and effective, it will take some time for the study gel to be allowed to be sold in the shops, but we will try to make sure this happens as quickly as possible.

Section 10. Clinical Considerations

This section presents information on clinical procedures performed in MTN-007. 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 13.

10.1 Baseline Medical and Menstrual History

The participant's baseline medical and menstrual (if female) history is initially collected and documented at the screening visit. It is then actively reviewed and updated, as necessary, at the enrollment visit. After the enrollment visit, the baseline medical and menstrual history should not be updated unless the participant recalls information at a later visit related to his/her medical history at baseline.

The baseline medical and menstrual history will ascertain a participant's medical history by major body systems, a participant's alcohol and drug use history, as well as specific rectal/GI symptoms a person may have experienced. The form will also be used to explore any medical conditions or medications that are deemed exclusionary for this study. The purpose of obtaining this information during screening and enrollment is to:

- Assess and document participant eligibility for the study
- Assess and document the participant's baseline medical conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up
- Monitor any potential adverse events associated with the use of the study product during the course of the study

The non-DataFax Participant-Reported Baseline Medical and Menstrual History form is a recommended source document for collecting baseline medical and menstrual history information; however, alternative site-specific history forms may be used. That is, a site may create its own source documentation.

When obtaining the baseline medical and menstrual history, it is not necessary to document the participant's lifetime medical history; rather, site staff should ask the participant to answer questions/describe conditions based on the time since he/she has became sexually active. "Sexually active" refers to the time point that the participant first had vaginal or anal sexual intercourse with another partner (this does not include oral sex). Additional guidelines to collecting the baseline medical and menstrual history are listed below:

- Use the list of body systems and conditions on pages 1-3 of the Participant-reported Baseline Medical and Menstrual History form as guide to probe for history related to each system and condition. For conditions that are not associated with the listed systems, record relevant history in the "other medical problem" section on page 6.

- Record symptoms, illnesses, allergies, and surgeries

- Record both chronic and acute conditions, and both ongoing and resolved conditions

- Document whether each condition is currently ongoing; for enrolled participants, conditions that are ongoing at the time of enrollment/randomization are transcribed onto the Pre-existing Conditions form. For ongoing recurrent conditions that are expected to be experienced during follow-up (e.g. headaches), the condition need not be present on the day of enrollment to be considered ongoing at the time of enrollment.

- For all ongoing conditions, assess and record the current severity of the condition per the DAIDS Toxicity Table, Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies). See Section 11 of this manual for further clarifications, guidelines, and tips for severity grading in MTN-007.

- Record information on the participant's use of alcohol and recreational drugs, including the specific substances used and dates and frequency of use (page 4 of the Participant-reported Baseline Medical and Menstrual History form). If the participant reports any diagnosed conditions associated with alcohol or drug use that are not recorded elsewhere, record the conditions and relevant details, including date of diagnosis and severity grade.

- If the participant has a known history of STI or RTI, these may be recorded in the "STI/RTI" items on page 4 of the Participant-reported Baseline Medical and Menstrual History form.

- For anal/colorectal/GI symptoms, each symptom listed on pages 5 and 6 of the Participant-reported Baseline Medical and Menstrual History form should be read aloud to the participant to actively ask him/her about each one.

- Record whether the participant has experienced any type of sexual assault; if so, document relevant details on page 6 of the Participant-reported Baseline Medical and Menstrual History form.

- Record any other obstetric (women only), gynecologic (women only), or reproductive problems and/or procedures, and relevant details (including severity grade for any ongoing conditions or problems) on page 6 of the Participant-reported Baseline Medical and Menstrual History form.

- *Women only*: For menstrual history information, including menstrual symptoms, non-menstrual genital bleeding, and description of usual menstrual cycle, complete all items on page 7 of the Participant-reported Baseline Medical and Menstrual History form.

- *Women only*: For pregnancy history (page 8 of the Participant-reported Baseline Medical and Menstrual History form), record the outcome, outcome date, and type of delivery for each pregnancy. Also record any congenital anomalies or other problems associated with each pregnancy, as well as the current vital status (alive or deceased) of all children born alive.

- *Women only*: For contraceptive history (page 7 of the Participant-reported Baseline Medical and Menstrual History form), record all contraceptive methods ever used by the participant and approximate dates of use for each method. Document any problems experienced with use of each method and any other relevant details. Current contraceptive methods should be transcribed onto the Concomitant Medications Log form.

- Document medications currently taken for all ongoing conditions on the Concomitant Medications Log form (or other site-specific source document) as described in Section 10.4.

10.2 Follow-up Medical and Menstrual History

It is necessary to update the participant's medical history at each follow-up clinic visit (and any interim visit) in order to determine whether previously reported conditions remain ongoing and whether new symptoms, illnesses, conditions, etc. have occurred since the last medical and menstrual history was performed. The non-DataFax form Participant-reported Follow-up Medical and Menstrual History form can used to gather this information. At each post-enrollment visit it is only necessary to record information that has occurred or changed since the previous visit.

10.3 Pre-existing Conditions

A key purpose of conducting the baseline medical and menstrual history, as well as the physical and rectal exams (described below), is to document participants' baseline medical conditions, for comparison with signs, symptoms and conditions that may be identified or reported during follow-up. All ongoing medical conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported *at* or *before enrollment* are considered pre-existing conditions.

For all participants enrolled in the study, all ongoing conditions recorded as pre-existing are to be thoroughly source documented and transcribed onto the Pre-existing Conditions case report form. This form is to be completed at the Screening Visit and reviewed/updated at the Enrollment Visit based on all screening and enrollment source documents including, but not limited to, the Baseline Medical and Menstrual History form, Physical Exam form, Rectal Exam form, Anoscopy and Sigmoidoscopy Results form, Laboratory Results form, and STI Laboratory Results form.

All pre-existing conditions noted at screening and enrollment must be graded though they are not considered to be adverse events. The purpose of grading a pre-existing condition is because the Pre-existing Conditions form serves as the "starting point" from which study clinicians must determine whether abnormal conditions, symptoms, signs and findings identified during follow-up are adverse events (AEs). By definition, pre-existing conditions are present prior to enrollment/randomization and are, therefore, not considered AEs. However, new conditions identified during follow-up that were not present at enrollment/randomization, and pre-existing conditions that increase in severity (increases to a higher grade) or frequency during follow-up, are considered AEs. Therefore, the clinician should record as much information as possible about the severity and frequency of any pre-existing condition in source documents as well as in the comments field of the Pre-existing Conditions form to best describe the condition at study entry. This allows for greater objectiveness in noting any grade increase of the pre-existing condition.

10.4 Concomitant Medications

The MTN-007 protocol requires site staff to document all medications taken by study participants beginning at screening and continuing throughout the duration of the study. This includes any prescriptions, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs and herbal and naturopathic preparations. All medications, drugs, supplements and preparations will be recorded on the Concomitant Medications Log.

It is helpful to ascertain the baseline medication information in the context of the baseline medical/menstrual history. Site staff should ask open-ended questions to elicit participant report of current medications, and use the information obtained in the medical/menstrual history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of her medical history, but does not spontaneously list any medications taken for headaches; ask if she takes any medications for headaches. Similarly, if a participant reports taking a medication for a condition that he inadvertently did not report when providing medical history information, add the condition to the baseline medical/menstrual history source document.

At each follow-up clinic visit, retrieve the participant's previously completed Concomitant Medications Log form, record any new medications provided to the participant by study staff, and actively ask the participant whether he/she is still taking all previously-recorded medications, at the same dose and frequency. Also actively ask whether the participant has taken any new medications since the last medical/menstrual history was taken. To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc. since his/her last medical history, ask whether he/she took any medications for those. Add all new information to the form in log fashion, using additional form pages as needed. If a participant reports taking a new medication for a condition that he/she inadvertently did not report when providing follow-up medical/menstrual history information, add the condition to his/her follow-up medical/menstrual history source document. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring all medications to all study visits.

10.5 Prohibited Medications and Products

For MTN-007 the following medications are prohibited from use during the study:

- Heparin (including Lovenox)
- Warfarin
- Plavix (clopidogrel bisulfate)
- Rectally administered medications (including over-the-counter preparations)
- Aspirin
- NSAIDS*
- Post-exposure prophylaxis
- Systemic immunomodulary medications
- Rectally administered products containing N-9
- Any drug associated with the increase likelihood of bleeding after mucosal biopsy
- Any other investigational drug

* If use of NSAIDS is reported by a participant prior to a study visit in which endoscopic examinations and/or biopsies are obtained, the study visit should be rescheduled. If the event this is not able to occur, the determination of action would be decided by an urgent PSRT consultation. Study product use may be discontinued at the discretion of the IoR/clinician in consultation with the PRST.

If a participant reports using a prohibited medication during the study, this must be recorded on the Concomitant Medications Log. Should a participant report using any of the above listed medications or products, study staff should consult the PSRT regarding product use.

10.5 Physical Exam

A physical exam is completed at the Screening, Enrollment, Treatment 1 and Final Clinic Visits. It should only be performed at the Treatment 2 Visit if it is clinically indicated. At all scheduled time points, physical exams should include the assessments listed in protocol section 7.11 and repeated below. 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 required physical exam components:

- Height (may be omitted after the Screening visit)
- Weight
- Vital Signs
  - Temperature
  - Pulse
  - Blood pressure
- General appearance
- Abdomen
- Other components as indicated be participant symptoms

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 (that are not exclusionary) identified at the Screening and Enrollment Visits should be recorded on the Pre-existing Conditions form. Abnormal findings found during physical exams performed during follow-up should be documented and/or reported as described in Section 11.

Physical exams may identify additional baseline medical 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 Baseline Medical History form and the Pre-existing Conditions form as well, since the condition was present at the time of enrollment.

10.6 Rectal Exams

Rectal exams are required at the Screening, Enrollment, Treatment 1, and the Final Clinic Visits. A rectal exam is performed at the Treatment 2 Visit only if clinically indicated. A basic rectal exam consists of a digital examination of the rectum as well as a visual inspection of the anus and surrounding area. In most cases, when a rectal exam is performed, rectal samples (swabs, sponges, etc.) are also collected.

Rectal exams must be performed in the order shown on the rectal exam Checklists. These checklists are in Section 7 of this SSP. Detailed procedural and documentation instructions are provided below.

Potential participants identified at screening with abnormalities of the colorectal mucosa, or colorectal symptoms that represent a contraindication to biopsy (in the opinion of the clinician) are not eligible for the study. For participants who enroll in the study, abnormal rectal exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits should be recorded on the Pre-existing Conditions form. Abnormal findings found during rectal exams performed during follow-up should be documented and/or reported as described in Section 11.

10.6.1 Anorectal Visual Inspection

Anorectal examinations are undertaken in a private examination room with a curtain drawn between the participant and the entrance door. Explain all procedures to the participant before and while performing them.

The participant should be undressed from the waist down, lying in the left lateral (decibitus/fetal) position on top of the examination table with the anal area exposed and at the lower edge of the table.

The anal and perianal area is visually examined and any abnormal finding(s) noted on the Rectal Exam CRF as well in chart notes.

10.6.2 Digital Rectal Exam

The clinician performs a digital rectal exam with Pre® Personal lubricant prior to the insertion of the anoscope to relax the anal sphincter and rule out gross obstructions or malformations that may prohibit anoscopy.

The right buttock is gently raised to allow visualization of the anus (the participant may do this if they wish). A lubricated (Pre® Personal lubricant) gloved finger is gently inserted and swept around the entire internal anal circumference. Any abnormal finding or unexpected discomfort should be noted on the Rectal Exam CRF as well in chart notes.

Note: In order to reduce the amount of mucosal trauma, this is an anal canal exam only and is not a full digital rectal exam with examination of the prostate.

10.6.3 Specimen Collection

Perform rectal specimen collection in the sequence specified on the rectal exam checklists in Section 7. Additional details are included below. For more information on specimen collection, processing and testing of rectal specimens, see SSP section 12.

Anorectal Swabs

Swabs will be collected for both GC and CT using the GenProbe Aptima detection system and rectal microflora using a port-a-cult.

A lubricated (Pre® Personal lubricant) anoscope is inserted into the anal canal until the anoscope 'wings' touch the anal verge. After removing the obturator, the GC/CT swab will be inserted into the rectal lumen that is visible at the end of the anoscope and rotated through 360 degrees and removed. The rectal microflora swab will be taken after the swab for GC/CT using the same technique.

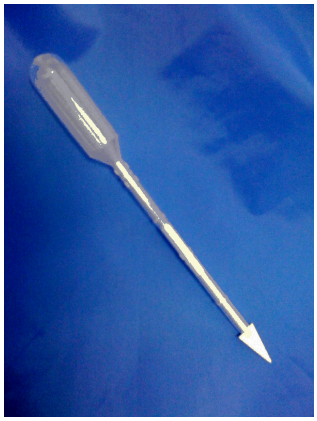
Rectal Sponge

Rectal Sponge Preparation

Approximately 45 minutes before the collection of the rectal sponge specimen through the anoscope, a clinician or staff member should prepare the materials (the insertion tube) as follows:

1. Obtain a disposable transfer pipette and cut off the end approximately 1 inch from the tip
2. Insert the stem of the sponge into the end of the pipette
3. Make sure that the stem of the sponge will fit the pipette snugly and will not dislodge during insertion or extraction from the rectal cavity.

Figure 10-1: Disposable Transfer Pipette Extension with Rectal Sponge



Using study provided lubricant (Pre® Personal lubricant), site clinician should lubricate the anoscope prior to insertion. The anoscope should then be inserted into the anal canal until the anoscope 'wings' touch the anal verge, then remove the obturator. After removing the obturator, place the sponge (attached to the pipette extension) through the anoscope into the rectum and hold (or leave) it against the rectal wall for 5 minutes. Remove the sponge, disengage the sponge with plastic stick from the plastic holder, and place the sponge into the appropriate tube. Note: The plastic holder refers to the transfer pipette used to make the stick longer and easier to manipulate. At visits when both swab(s) and sponge are collected, they may be taken sequentially with the GC/CT swab taken first during the same anoscopic examination.

Rectal Lavage

Rectal Lavage is a procedure in which involves instilling a solution to wash the rectum. The effluent is collected for analyses, such as inspection for any epithelial cells that may have sloughed off of the rectal mucosa.

With the participant in the left lateral position, insert the lubricated (Pre® Personal lubricant) nozzle of the 120ml enema bottle containing Normasol into the rectum. When the nozzle is fully inserted, squeeze the bottle to instill the solution into the rectum. Ask the participant to hold the fluid for at least 3-5 minutes, then ask the participant to use the restroom and dispel the fluid and stool into the collection 'hat', taking care not to urinate or place paper in the 'hat'.

Samples of effluent (for lavage studies) and stool (for measurement of fecal calprotectin) will be taken from the 'hat'.

10.6.4 Sigmoidoscopy

- Check to ensure the sigmoidoscope is switched on, suction is on, and air flow is working.
- With the participant in the left lateral decubitus position, the sigmoidoscope tip is lubricated with Pre® Personal lubricant and gently inserted to 15 cm from the anal verge.
- Introduce endoscopic 'jumbo' forceps into the sigmoidoscope channel and commence mucosal specimen collection at between 12-15 cm from the anal verge. The forceps need to be carefully washed in water between every biopsy.

- Biopsy 1: Shake the biopsy into a 10% formalin tube for histology
- Biopsy 2: Shake the biopsy into a labeled RNA later tube for gene expression determination
- Biopsy 3 and 4: Shake each biopsy into a labeled RNA later tube for cytokine determination
- Biopsy 5, 6 and 7: Shake each biopsy into a RPM tube for T cell phenotype

- Remove the sigmoidoscope.

10.6.5 Anoscopy

- Ensure the high-resolution anoscope is swiched on, height adjusted so that the circular field of light has the anal opening centered, and magnification is set to x 16.

- A clear plastic anoscope is inserted as described above.

- Using the same endoscopic biopsy forceps used for sigmoidoscopic biopsies, 7 rectal biopsies are taken by sampling the most dependent area first to avoid blood obscuring the field.

- Biopsy number and tube placements are as above for sigmoidoscopic biopsies, and again forceps are washed between each biopsy in water.

- Rectal blood is mopped using proctoswabs after the biopsies have been taken, and the anoscope is removed. Excess lubricant is wiped from the anal margin.

- Vital signs are re-taken are obtained and documented in chart notes.

Section 11. Adverse Event Reporting and Safety Monitoring

11.1 Definitions

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-007. Please also refer to Section 8 of the MTN-007 Protocol Version 2.0 dated 13 August 2010 and the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010).

11.1.1 Adverse Event

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an adverse event (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-007 protocol specifies that any untoward medical occurrence experienced by a participant after enrollment, which begins at the time of random assignment, is considered an AE, regardless of the study group to which the participant is assigned (i.e. "gel" or "no gel").

In MTN-007, all AEs are reportable. That means that all AEs should be recorded on the Adverse Experience (AE) Log case report form (Section 13) and the form should be faxed to the MTN Statistical and Data Management Center (SDMC) via DataFax. All AEs should also be documented in source documents. Each site's SOP for source documentation (see Section 3) should define the extent to which the AE Log form will be used as a source document. Site-specific delegation of duties documentation should designate study staff authorized by the Investigator of 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.

Medical conditions, problems, signs, symptoms and findings identified prior to randomization are considered pre-existing conditions. Such conditions should be documented in the source documents (Section 3), which may include the Baseline Medical and Menstrual History non-DataFax form, the Rectal Exam form, lab forms, etc., and reported on the Pre-Existing Conditions case report form (Section 13). Pre-existing conditions must be graded because if the condition worsens after randomization; the worsened condition is considered an AE and is reportable on the AE Log form. Pre-existing conditions are assigned severity grades just like AEs (see Section 11.3 below), so the clinician can evaluate and document if the condition worsens after study enrollment (increases in frequency or severity), in which case it would be reported as an AE.

11.1.2 Serious Adverse Event

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
  - *Note:* Per ICH SAE definition, hospitalization itself is not an adverse event, but is an outcome of the event. Thus, hospitalization in the absence of an adverse event is not regarded as an AE, and is not subject to expedited reporting. The following are examples of hospitalization that are not considered to be AEs:
    - Protocol-specified admission (e.g., for procedure required by study protocol)
    - Admission for treatment of target disease of the study, or for pre-existing condition (unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator)
    - Diagnostic admission (e.g., for a work-up of an existing condition such as persistent pretreatment lab abnormality)
    - Administrative admission (e.g., for annual physical)
    - Social admission (e.g., placement for lack of place to sleep)
    - Elective admission (e.g., for elective surgery)
- Results in persistent or significant disability/incapacity
- 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 be considered serious.

SAEs are a subset of all AEs. For each AE identified in MTN-007, an authorized study clinician must determine whether the AE meets the definition of SAE. The Adverse Experience Log case report form includes an item (item 8) to record this information. Throughout the entire follow-up period, all SAEs – regardless of relatedness – will be recorded on the Adverse Experience Log CRF.

11.1.3 Expedited Adverse Event

Expedited Adverse Events (EAEs) are AEs that meet criteria specified in the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010) as requiring additional reporting for rapid review and assessment by the CONRAD and the DAIDS Medical Officers (MOs). For MTN-007, the AEs that must be reported in an expedited fashion include all SAEs occurring in participants assigned to "gel", starting at the Treatment 1 Visit up through the participant's Follow Up Phone Assessment/Termination Visit, regardless of the relationship to the study agent(s). All EAEs must be reported to the DAIDS Regulatory Support Center (RSC) Safety Office, also known as the DAIDS Safety Office, via DAIDS Adverse Event Reporting System (DAERS). Once the Termination Visit has been completed, if the site becomes aware of any suspected, unexpected serious adverse reactions (SUSAR) and/or pregnancy outcomes that meet criteria for expedited reporting, these events will also be expeditiously reported.

EAE reporting is undertaken for participants assigned to a "gel" group only. No EAEs are reported for participants assigned to the "no gel", also referred to as "no treatment", group.

All EAEs must be reported using the DAERS internet-based reporting system. If an EAE report needs to be modified or updated, or an EAE report submitted in error needs to be withdrawn, this can also be done through DAERS. For questions about DAERS, contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself. Information about DAERS is also available on the RSC website at http://rsc.tech-res.com. All EAEs will be reported via DAERS Reporting System within three (3) reporting days of site awareness (the site's recognition that the event fulfills the criteria for expedited reporting) to the DAIDS Safety Office through their Regulatory Support Center (RSC) according the procedures specified in the DAIDS EAE manual.

If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Reporting Form (EAE Reporting Form) and submitted as specified by the DAIDS EAE Manual. This form may be found on the Regulatory Support Center (RSC) website at http://rsc.tech-res.com.

For questions or other communications regarding submission of EAE Reports, see below.

Website:	http://rsc.tech-res.com
Office Phone:	301-897-1709 or toll free in the US: 800-537-9979
Office Fax:	301-897-1710 or toll free in the US: 800-275-7619
Office Email:	DAIDSRSCSafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM ET

All EAEs must also be reported on the Adverse Experience Log case report form. The AE Log case report form includes an item (item 9) to record if the AE is also being reported as an EAE. When completing AE Log CRFs and DAERS report or EAE form, 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 EAEs submitted to the DAIDS Safety Office will be compared with AE Log forms received at the MTN SDMC to ensure that all reports that should have been received by both DAIDS Safety Office and the SDMC have been received and that the details recorded on each form are consistent. For SAEs experienced by no gel participants as well as experienced by gel participants prior to the Treatment 1 Visit (and as such, not reported as EAEs), information from the AE Log CRF will be forwarded by the MTN SDMC to the DAIDS MO.

11.2 Adverse Event Terminology

Both the Adverse Experience Log case report form and the DAERS report or EAE form require site staff to assign a term or description to each AE. Whenever possible, a diagnosis should be reported, rather than a cluster of signs and/or symptoms. 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. When relevant, an anatomical location should be included in the term or description.

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 (such as 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.

Further tips and guidelines for assigning AE terms are as follows: use medical terms whenever possible, use correct spelling for all terms, and do not use abbreviations. Additional instructions on completion of AE Log forms can be found in Section 13 (both on the back of the AE Log form and in Section 13.6).

11.3 Adverse Event Severity

The term severity is describes as the intensity of an AE (that is, the grade or level for a specific event such as mild, moderate, severe, or life-threatening. Importantly, severity is not the same as seriousness, which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning (ICH E2A).

The DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009), Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies) will be the primary tools for grading adverse events for this protocol. Adverse events not included in those tables will be graded by the DAIDS AE Grading Table, Version 1.0 December 2004 (Clarification dated August 2009). In cases where an AE is covered in multiple tables, Addendum 3 (Rectal Grading Table for Use in Microbicide Studies) will be the grading scale utilized. The grading tables are available at http://rsc.tech-res.com/safetyandpharmacovigilance/default.aspx.

There are 5 severity grades that can be assigned to AEs, which are defined as follows:

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Potentially Life-threatening
Grade 5 = Death

Further clarifications, tips and guidelines for grading the severity of AEs are as follows:

- For the grading of clinical AEs not specified in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events or in the protocol, sites are to use the 'Estimating Severity Grade' on page 3 of the of the DAIDS grading table
- If the severity of an AE could fall under either one of two grades (e.g., the severity could be a grade 2 or a 3), the higher of the two grades should be assigned
- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, assign the highest severity grade of each of the signs and symptoms to the AE
- Seasonal allergies should be graded according to the 'Estimating Severity Grade' row of the Toxicity Table
- Glycosuria should be graded per the "proteinuria" row of the Toxicity Table

11.3.1 Assigning Severity Grades for Laboratory Assays on Case Report Forms

For some lab assays, the severity grade range is calculated using a value from the DAIDS Toxicity Table and a local normal range. When grading laboratory values for which the Toxicity Table specifies the use of a multiple of the upper limit of normal (ULN), 'normal' values are defined according to local age-adjusted institutional values.

For example, Grade 1 for total bilirubin is 1.1–1.5 times the site lab upper limit of normal (ULN). There will be times when the calculated severity range will have more significant digits than the reported lab value, which can lead to confusion regarding which severity grade to assign.

When working with calculated severity grade ranges, remember the following:

1. Rounding is permitted only when recording lab values on a CRF in order to match the level of precision allowed on the CRF.

2. When calculating a severity grade range, never round on interim steps.

3. Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).

4. If the calculated severity grade range has more significant digits than the lab value, do not round the calculated range values. Instead, treat all missing digits in the lab value as zeros.

- Example: Total bilirubin = 1.4 mg/dL, site ULN = 1.3 mg/dL

	DAIDS Toxicity Table Grade Range	Site-specific Grade Range
Grade 1	1.1–1.5 x ULN	1.43–1.95 mg/dL
Grade 2	1.6–2.5 x ULN	2.08–3.25 mg/dL

The site-specific grade range is accurate to the hundredths place (because 1.1 x 1.3 = 1.43 and 1.5 x 1.3 = 1.95, etc.). Treating the hundredths place of the total bilirubin value as a zero gives us a value of 1.40.

The lab value (1.40) falls below the minimum calculated value for Grade 1 (1.43). Do not assign a severity grade or report as an Adverse Experience.

5. If the lab value falls between two calculated severity grade ranges, assign it the higher grade as stated in the DAIDS Toxicity Table General Instructions (page 1).

- Example: Total bilirubin = 2.0 mg/dL, site ULN = 1.3 mg/dL

  As in the example above, the site-specific grade range is accurate to the hundredths place. The hundredths place of the total bilirubin value is treated as a zero, giving us a value of 2.00.

The lab value (2.00) falls between the maximum calculated value for Grade 1 (1.95) and the minimum for Grade 2 (2.08). Therefore, this value should be assigned the higher grade (Grade 2).

11.4 Adverse Event Relationship Assessment

For each AE indentified in MTN-007, the study clinician must assess the relationship of the AE to the study product, based on the temporal relationship of AE onset to study drug administration, the pharmacology of the study product and his/her clinical judgment. The categories of relatedness that will be used to assess the relationship of all AEs to study product are:

- Related: There is a reasonable possibility that the AE may be related to the study agent(s)

- Not related: There is not a reasonable possibility that the AE is related to the study agent(s)

When assessing relationship, the study products in MTN-007 that should be considered are the three gels and the applicators in which these gels are packaged. For participants assigned to gel, any AE thought to be related to an applicator should be documented as such by choosing the "Related" category and using descriptive text, comments, or other notations to indicate that the presumed relationship is with the applicator. For participants assigned to "no gel" (no treatment), this item will always be "Not Related" and using descriptive text or comments noting relationship is not related because participant is "no gel."

11.5 Follow-up Information on Adverse Event

All AEs identified in MTN-007 must be followed clinically until the AE resolves (returns to baseline) or stabilizes. In addition to performing protocol-specified assessments, at each visit, an authorized study clinician should review all previously reported ongoing AEs to evaluate and document in the participant's chart notes the current status.

A new Adverse Experience Log CRF is NOT required when submitting follow-up information for a previously reported AE. Rather, the existing CRF is updated and resubmitted. However, if an AE increases in severity or frequency (if it worsens), it must be reported as a new AE on a new AE Log form. The onset date on the AE Log form will be the date that the severity or frequency increased. Note that a decrease in severity should not be reported as a new AE. For additional instructions, see Section 13.

The requirements for submission of follow-up information on EAEs are specified in Section 4.3 of the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0 dated January 2010). As specified therein, for the circumstances listed below regarding an EAE reported to DAIDS, the site is required to submit an updated report to DAIDS as soon as significant additional information becomes available. Requirements include:

- An updated report documenting the stable or resolved outcome of the AE, unless the initial report included a final outcome,
- Any change in the assessment of the severity grade of the AE or the relationship between the AE and the study agent, or

- Additional significant information on a previously reported AE (e.g., cause of death , results of re-challenge with the study agent(s)).

Note: If Information regarding an EAE is updated (i.e., onset date, relationship to study product), the corresponding AE Log case report form should also be updated and resubmitted if any data recorded on the AE Log form has been updated. It should also be noted that if a previously-reported AE increases in severity grade, a new AE Log page for the new (higher grade) AE should be completed and submitted.

11.6 Outcome of Adverse Events, Review of AE Reports, and Study Physician Assessment and Signature

The site must follow the progress of each reported adverse event and record eventual outcomes in the source documentation. In many cases the final outcome of an AE will not be available when the AE Log form is first completed and faxed to SCHARP DataFax. In such cases, the AE Log form should be updated when the final outcome becomes available. If the AE is still continuing at the time of the Follow-up Phone Assessment Visit/Termination Visit, item 6 ("Status/Outcome") of the AE Log form should be updated to "Continuing at end of study participation". Any AE continuing at the Follow-up Phone Call Assessment Visit/Termination Visit should be followed clinically until resolution or stabilization, and this should be documented in chart notes only (the AE Log form should not be updated once the participant has terminated from the study).

Site staff should carefully review ALL documentation regarding an adverse event to ensure consistency and accuracy. This includes the source documentation, the AE Log CRF and the EAE Form. Site staff should be sure that onset dates, severity grades and all other details are consistent. 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.

The Investigator or designee should carefully review all laboratory abnormalities relevant to the participant's health available since the last visit to identify any adverse events or health problems. Documentation of this review is required by initialing and dating each page of lab results.

The severity of all lab abnormalities will be graded and recorded in the source documentation. Results of protocol-specified local laboratory results will also be reported on the Lab Result DataFax CRF. Sites should document other results if any, in visit chart note, or in other designated site-specific document. Through the participant's study involvement, lab abnormalities that meet the criteria for expedited reporting to DAIDS will be reported separately on the Adverse Experience Log CRF and reported to DAIDS via the DAERS Reporting System.

A study clinician listed on the FDA Form 1572 must assess each participant and record the details of all adverse events in the source documentation and complete or carefully review the information transcribed onto the AE Log CRF.

A study physician listed on the FDA Form 1572 must review and verify the data on the DAERS report or EAE form for accuracy and completeness. This physician also makes the site's final assessment of the relationship between the study product and the adverse event. This physician must electronically sign the completed DAERS report or EAE 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 reporting days.

11.7 Reporting Recurrent Adverse Events

If a resolved adverse event that was previously reported on the AE Log CRF later recurs, the AE is considered a new adverse event and a new AE Log CRF must be completed.

Likewise, if a resolved EAE that was previously reported to DAIDS later recurs at a level requiring expedited reporting, the EAE must be reported as a new EAE Report to the DAIDS Safety Office.

11.8 Social Harms

In addition to medical adverse events, participants may experience social harms – any non-medical adverse consequence experienced as a result of a person's participation in a 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 harm occurs, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. There is no CRF for the reporting of social harms. However, in addition to documenting the social harm in the source files, the Investigator of Record will report any social harm, in his/her judgment, to be serious or unexpected to the IRB on at least an annual basis. Study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

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 11.1.3 above. Also report the issue or problem to all responsible IRBs, if required per IRB guidelines.

• Ask the participant to articulate his/her thoughts on what can/should be done to address the problem, including what he/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 him/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 return to baseline.

• Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.

• Consult the MTN-007 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-007 PSRT.

11.9 Safety Distributions from DAIDS

Sites will receive product- and safety-related information throughout the period of study implementation from DAIDS through its Regulatory Support Center and/or the MTN Coordinating and Operations Center. The information distributed may include:

- Safety Reports and Memos
- Updated Investigator Brochures and Package Inserts
- Other safety updates and documents.

Each distribution will indicate in the cover note how the information is to be handled. In many cases, this information must be submitted to all responsible IRBs for their information and retained in the site regulatory files. It is important for all relevant clinical staff to be provided copies of this information or be notified of their receipt and have access to them for careful review. Safety distributions do not require IRB approval; however, acknowledgement of receipt is desirable. Cover letters for these (and all) IRB submissions should specify the name and date of all attachments.

11.10 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-007 protocol for a complete description of the participant safety monitoring procedures in place for MTN-007. Also refer to Section 15 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-007 safety monitoring procedures.

Participant safety is of utmost concern. 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 DAERS report or EAE form 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:

- Clinical Affairs staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data quality control notes (clinical queries) to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be issued to site staff for resolution on an ongoing basis throughout the period of study implementation.

- The DAIDS PSP Medical Officer and CONRAD Medical Officer will review all DAERS report or EAE form received for MTN-007 and follow up on these reports with site staff, the MTN-007 Protocol Team, and drug regulatory authorities when indicated.

- The MTN-007 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for MTN-007 by the MTN SDMC. The PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns (See Section Appendix III for more details).

Management of study product dosing (temporarily holding or permanently discontinuing either study product dosing) relative to the occurrence of toxicities must follow the standard toxicity management procedures. Site staff should seek the advice and counsel of the PSRT on these matters.

11.11 Protocol Safety Review Team (PSRT)

11.11.1 Roles and Responsibilities of the PSRT

Per the MTN-007 protocol, the roles and responsibilities of the MTN-007 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 for the first six months of the study. Thereafter, 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).

2. Respond to Investigator queries regarding permanent discontinuation of product use (protocol Section 9.4). The protocol specifies criteria for permanent discontinuation of further study product use. These situations include, but are not limited to consultation on:

   (a) Study product-related toxicity requiring discontinuation of study product(s)
   (b) Request by participant to terminate study product(s)
   (c) Clinical reasons determined by the physician
   (d) HIV infection
   (e) Pregnancy or Breastfeeding

   When the IoR discontinues study product(s) due to study product-related toxicity, or any other clinical reason that is not specified in the protocol as criteria for permanent discontinuation, the PSRT should be notified immediately.

   There are other situations when the IoR would discontinue product and then submit a PSRT query form to notify the PSRT of product discontinuation and obtain further product use management guidance, such as:

   (a) Study product-related toxicity per Sections 9.3 and 9.5 of the MTN-007 protocol.
   (b) Use of a prohibited medication
   (c) Participants are unable or unwilling to comply with required study procedures;
   (d) Otherwise might put participant at risk or the safety and well-being of the participant may be compromised by continuing product use.

3. Respond to Investigator queries regarding study eligibility and general AE management and reporting (not necessarily related to product use).

4. Respond to Investigator requests for participant withdrawal from the study (protocol Section 9.6).

11.11.2 PSRT Composition

The following individuals currently comprise the MTN-007 PSRT:

- Ian McGowan, Protocol Chair
- Kenneth Mayer, Protocol Co-Chair
- Jeanna Piper, DAIDS PSP Medical Officer
- Jill Schwartz, CONRAD Medical Officer
- Katherine Bunge, MTN Safety Physician
- Devika Singh, MTN Safety Physician
- Yevgeny Grigoriev, SDMC Clinical Affairs Safety Associate

Ideally all of the above-listed PSRT members will take part in routine PSRT conference calls; however a quorum of at least two members, the DAIDS PSP Medical Officer (or designee) and an MTN Safety Physician, must take part in all calls.

If a quorum is not present, the call may be deferred until the next scheduled call time unless a quorum member requests a more immediate call.

The MTN CORE (FHI) Clinical Research Managers and SDMC (SCHARP) Project Managers will also participate in and facilitate PSRT calls and reviews. The DAIDS PSP Program Officer(s), MTN CORE Pharmacist and Co-Sponsors also may attend calls as observers.

11.11.3 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 within a week prior to each PSRT conference call. Tabulations will be generated for all study participants combined (i.e., across all study regimen groups). Pending final confirmation from the PSRT, the following events will be included in the standard safety data reports, regardless of relationship to study product:

- Cumulative listing of all study expedited adverse events (EAEs) and serious adverse events (SAEs)
- Summary of uncoded adverse event coding progress
- New adverse events by body system/MedDRA preferred term and severity
- New adverse events by body system/MedDRA preferred term and relationship to study product
- Cumulative adverse events by body system/MedDRA preferred term and severity
- Cumulative adverse events by body system/MedDRA preferred term and relationship to study product
- Summary of pregnancies and pregnancy outcomes

During PSRT conference calls, the DAIDS Medical Officer will summarize any additional DAERS report or EAE form received at the DAIDS Safety Office after the cut-off date for inclusion in the SDMC PSRT report.

11.11.4 PSRT Communication

An email distribution list will be used to facilitate communication with the PSRT. Queries and communications with the PSRT should be sent via email to mtn007safetyMD@mtnstopshiv.org. All safety data summary reports from the SDMC, all PSRT queries from study sites, and all query responses from the PSRT will be distributed via this alias.

A standard PSRT query form (Appendix III) will be used to elicit sufficient information to allow the PSRT to make an informed determination and respond to each query. The Protocol Safety Physicians will review the PSRT query form, add their recommendations to the document, and post the updated document to the message board. Please note that site staff should NOT post queries directly to ATLAS; rather, they must e-mail the queries to the Protocol Safety Physicians per instructions on the PSRT Query Form. The PSRT Query Message Board is for the sole use of the MTN-007 PSRT. Through SCHARP/ATLAS, the PSRT member can configure her or his preferences to receive e-mail notifications automatically from the message board when a new query or response is posted.

Note: Replying to an e-mail notification from Atlas DOES NOT add the response into the discussion on ATLAS. To post a response, you must log into Atlas, navigate to the appropriate query discussion page, and post your response. The MTN-007 PSRT Query Message Board is password-protected. Access to the message board is limited to members of the SCHARP ATLAS group and to users who are subscribed to the PSRT alias list (mtn007psrt@mtnstopshiv.org).

Once all responses have been submitted and discussed, the Safety Physician will inform the site of PSRT decision and then file the resolved query online. If a PSRT member cannot access the Message Board via a mobile device, they are to email the safety physicians to inform them of their problem and the Safety Physicians will return the email with the query attached. To ensure a timely PSRT response, the MTN Safety Physician and DAIDS Medical Officer have ultimate responsibility for providing a final response to the query (via email) within three business days

after receipt of the query (unless a more urgent response is requested by the site). 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 MTN Safety Physicians and the DAIDS Medical Officer on behalf of the PSRT.

In the event that the protocol team or PSRT has serious safety concerns, the protocol team or PSRT will request a review of the data by the MTN Study Monitoring Committee (SMC). While site staff are not typically involved in these reviews, site staff should be aware that the SMC may make recommendations to DAIDS and/or the MTN leadership that could affect the study and study sites in significant ways. These decisions are based on detailed review of the available study data and careful consideration of ongoing participant safety and study viability.

Section Appendix I

(DAIDS Female Genital and Rectal Grading Tables for Use in Microbicide Studies)

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004, Addenda 1 and 3 can be found at:
http://rsc.tech-res.com/safetyandpharmacovigilance/

Section Appendix II

DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
(Clarification dated August 2009)
This table can be found at http://rsc.tech-res.com/safetyandpharmacovigilance/.

Section Appendix III
MTN 007 Protocol Safety Review Team Query Form

Instructions: Email completed form to MTN Safety Physicians at mtn007safetymd@mtnstopshiv.org. It is important to complete all fields so the PSRT has all information needed to respond to your query.

Site: **Query Date (dd-MMM-yy):**

Completed by: **Email address:**

PTID: **Participant Age** (in years):

Reason for Query:
- ☐ Product use consultation:
  - ☐ Should use of study product be permanently discontinued?
- ☐ Request for consultation on AE management
- ☐ Request to withdraw participant from the study
- ☐ 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 product:
- ☐ Related
- ☐ Not Related

Current study product administration:
- ☐ No change
- ☐ Permanently discontinued
- ☐ Not Applicable

Has this AE been reported on a SCHARP AE Log form?
- ☐ Yes
- ☐ No

Has this AE been reported as an SAE?
- ☐ 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

MTN 007 Protocol Safety Review Team Query Form (Continued)

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

Comments: Provide additional details relevant to this query. If product use has been discontinued, include date of last reported product use prior to the discontinuation (per participant report).

End of Form for Site Staff. Email completed form to the MTN-007 Protocol Safety Physicians at mtn007safetymd@mtnstopshiv.org. If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians and/or the MTN CORE (mtn007mgmt@mtnstopshiv.org) for assistance as soon as possible.

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 12. Laboratory Considerations

12.1 Overview and General Guidance

This section contains information on the laboratory procedures performed in MTN-007.

As transmission of HIV and other infectious agents can occur through contact with contaminated needles, blood, blood products, rectal, 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 website:

• http://www.cdc.gov/ncidod/dhqp/bp_universal_precautions.html

Some laboratory procedures will be performed in the study site clinic or laboratory and others in the MTN Network Laboratory (NL). 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 QC procedures prior to performing the tests for study purposes; training documentation should be available for inspection at any time.

All site laboratories will be monitored by the MTN NL which will utilize information from DAIDS monitoring groups (PNL, IQA, VQA, etc.) to monitor and certify laboratories for testing. US sites that utilize Clinical Laboratory Improvement Amendment (CLIA) certified laboratories for testing will be able to substitute a valid CLIA certificate as documentation of the quality of the work at the laboratory.

Table 12-1
Overview of Laboratory Testing Locations, Specimens,
And Methods for MTN-007

Test	Testing Location	Specimen Type	Tube/Container	Kit/Method
Urine pregnancy test	In Clinic	Urine	Plastic screw top cup	Quidel Quick Vue or Fisher Sure-Vue
Urine NAAT for Gonorrhea and Chlamydia	Local Lab	Urine	Urine Preservation Tube (UPT)	GenProbe Aptima or BD Probetec
Dipstick Urinalysis	In Clinic	Urine	Plastic screw top cup	Bayer Multistix® 10 SG or Bayer Uristix 4
Complete blood count w/differential and platelets	Local CLIA Lab	Whole Blood	EDTA tube	Not specified
Chemistries (BUN, Creatinine, ALT, AST)	Local CLIA Lab	Serum or plasma	Consult local lab requirements	Not specified
Syphilis RPR (confirmatory test as needed)	Local CLIA Lab	Serum or Plasma	Red or Purple top tube	Not specified
HIV antibody screen and Western Blot	Local CLIA Lab	Plasma or whole blood (serum acceptable)	EDTA or plain tube	FDA approved tests
HBsAg	Local CLIA Lab	Serum	SST or plain tube	Not specified
HSV-1 and HSV-2 IgG Serology	Local CLIA Lab or MTN NL	Serum	SST or plain tube	Not specified
Plasma archive	Site Lab	Plasma	EDTA tube	N/A
Rectal NAAT for Gonorrhea and Chlamydia	Local CLIA Lab or MTN NL	Anorectal swab	Transport tube	GenProbe Aptima or BD Probetec
Rectal microflora	MTN NL	Rectal swab	Port-a-cul Tube	Culture
Epithelial sloughing	MTN NL	Rectal effluent	Specimen pan	MTN NL protocol
Histology	MTN NL	Rectal biopsies	Vial with 10% formalin	N/A
Cytokine RT PCR	MTN NL	Rectal biopsies	Cryovial with RNA*later*	MTN NL protocol
Mucosal T cell phenotyping	MTN NL	Rectal biopsies	Tube with cRPMI	MTN NL protocol
Cytokines	MTN NL	Rectal sponge	Cryovial	Luminex
Fecal Calprotectin	Genova Diagnostics	Stool	Genova container	Genova protocol
Mucosal gene expression array	MTN Immunology Core	Rectal biopsies	Cryovial with RNA*later*	MTN Immunology core protocol

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	18	Red Top: 12	BUN, Creatinine, ALT, AST RPR, HBsAg, HSV serology
		Purple Top: 6	CBC w/diff and platelets, HIV-1 serology
Enrollment	10	Red Top: 4	HSV serology, *RPR
		Purple Top: 6	*HIV-1 serology, Plasma archive
Final Clinic Visit	14	Red Top: 8	BUN, Creatinine, ALT, AST RPR
		Purple Top: 6	CBC w/ diff and platelets, HIV-1 serology
Early Termination Visit	14	Red Top: 8	BUN, Creatinine, ALT, AST RPR
		Purple Top: 6	CBC w/ diff and platelets, HIV-1 serology
Interim Contacts and Visits	14	Red Top: 8	BUN, Creatinine, ALT, AST RPR
		Purple Top: 6	CBC w/diff and platelets, HIV-1 serology

**Notes: Additional blood may be collected for any clinically indicated testing. Red top tubes contain no additive. Purple top tubes contain EDTA.*

Ideally, one method, one type of test kit, and/or a 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 test kit must be used after study initiation, site laboratory staff must perform a validation study of the new method or test prior to implementing a change in methods. The MTN NL must be notified before implementing the change and the MTN NL can provide further guidance on validation requirements. Similarly, the MTN NL must be notified of changes to normal lab ranges.

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.

This section of the MTN-007 SSP manual gives basic guidance to the sites, but is not an exhaustive procedure manual for all laboratory testing. This section must be supplemented with Standard Operating Procedures. The MTN NL is available to assist in the creation of any SOPs upon request. Essential SOPs include but are not limited to:

- SOPs created by the site
    - Specimen Collection and transport*
    - Chain of Custody *
    - Urine Dipstick *

*Must be approved by the MTN NL for study activation

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 of specimen collection should also be included on the label. If the date is handwritten, it should be in indelible ink (such as a Sharpie pen).

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. Specimens that are sent to the NL or are archived at the site will be entered into LDMS and labeled with LDMS-generated labels.

12.3 Procedures for Specimens that can not be Evaluated

When possible, specimens will be redrawn or recollected if it is found that they cannot be evaluated per site SOP's. The site will monitor specimen management problems as part of ongoing Quality Assurance. In cases where additional specimens need to be recollected due to a laboratory error (lost or broken specimen or clerical error) or a clinic error (clerical error), a protocol deviation form may 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 to track the collection, storage, and shipment of eight types of specimens in MTN-007: plasma for archive, rectal microflora, epithelial sloughing, biopsies for histology, cytokine RT PCR, mucosal T cell phenotyping, mucosal gene expression, and sponges for cytokines. See Table 12.4 for further information.

Detailed instructions for use of LDMS are provided at: https://www.fstrf.org/ldms (may require a password).

The site 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. The site 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-007 may be directed to Pam Kunjara 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 e-mail 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 (address shown in table 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

If a response is not received within 15 minutes after emailing LDMS 1, try emailing LDMS 2, then finally, LDMS 3.

Table 12-3
LDMS User Support Paging Details

Pager	Email Address
LDMS 1	ldmspager1@fstrf.org
LDMS 2	ldmspager2@fstrf.org
LDMS 3	ldmspager3@fstrf.org

The 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 the 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., blood 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 007 Specimens

The table below should be used as a guide when logging in 007 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
Plasma Archive	BLD	EDT	PL1	N/A	3.0	1.5	ml
Rectal Microflora	REC	NON	SWB	N/A	Variable	0.1	ml
Rectal sponge for cytokines	REC	PBS	SPG	N/A	Variable	1	Ea
Epithelial Sloughing	REC	NOR	LAV	PFM	Variable	variable	ml
[1] Biopsies for cytokine Anoscope 9 cm	ARB	RNL	TIS	N/A	2	1	Ea
[2] Biopsies for Gene Expression Anoscope 9 cm	ARB	RNL	TIS	N/A	1	1	Ea
Biopsies for Mucosal T cell phenotyping Anoscope 9 cm	ARB	RPM	TIS	N/A	3	3	Ea
Biopsies for Histology Anoscope 9 cm	ARB	FOR	TIS	N/A	1	1	Ea
[1] Biopsies for cytokine Sigmoidoscopy 15 cm	FSR	RNL	TIS	N/A	2	1	Ea
[2] Biopsies for Gene Expression Sigmoidoscopy 15 cm	FSR	RNL	TIS	N/A	1	1	Ea
Biopsies for Mucosal T cell phenotyping Sigmoidoscopy 15 cm	FSR	RPM	TIS	N/A	3	3	Ea
Biopsies for Histology Sigmoidoscopy 15 cm	FSR	FOR	TIS	N/A	1	1	Ea

1, 2: Specify Test Setup in LMDS Specimen Management Module (this is only for biopsy cytokine and biopsy gene expression)

- After creating aliquots in LDMS, right click on an aliquot
- Select "Test Setup"; this will bring up a dialogue box.
- Select either Cytokines or Gene Expression depending on the aliquot.
- Click save. When LDMS prompts that the changes have been saved, click Done to exit the dialogue box.
- In the "Other Spec ID" field of the aliquot line (between "Cond" and "Group ID") enter either CYK for Cytokines or GENE for Gene Expression. Click Save.

BLD: Whole Blood
EDT: EDTA
PL1: Single spun Plasma
REC: Rectal
NON: None
SWB: Swab
SPG: Sponge
PBS: Phosphate Buffered Saline
NOR: Normosol-R
LAV: Lavage
PFM: Paraformaldehyde
ARB: Rectal biopsy by anoscope
FSR: Rectal biopsy by Flexible sigmoidoscopy
TIS: Tissue
RPM: cRPMI media
RNL: RNAlater
FOR: Formalin

Table 12-5
Specimen Shipping Summary

Specimen	Use LDMS?	Ship to:	Shipping schedule
Rectal Microflora	Yes	MTN NL - Pittsburgh	Shipped daily and refrigerated on ice packs
Rectal effluent for Epithelial Sloughing	Yes	MTN NL - Pittsburgh	Shipped daily and refrigerated on ice packs
Biopsies for Histology	Yes	MTN NL - Pittsburgh	Shipped daily ambient or refrigerated on ice packs
Biopsies for Mucosal T cell Phenotyping	Yes	MTN NL - Pittsburgh	Shipped daily and refrigerated on ice packs
Rectal sponge for Cytokines	Yes	MTN NL - Pittsburgh	Batched and shipped frozen on dry ice
Biopsies for Cytokine RT PCR	Yes	MTN NL - Pittsburgh	Batched and shipped frozen on dry ice
Biopsies for Mucosal Gene Expression Array	Yes	MTN Immunology Core - Seattle	Batched and shipped frozen on dry ice
Rectal Stool for Fecal Calprotectin	No	Genova Diagnostics	Shipped daily at ambient temperature (Friday collected specimens are shipped on Monday)

12.5 Urine Testing for Urinalysis, Pregnancy, Chlamydia and Gonorrhea

The urine tests performed at the 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 aliquots will be made 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 and then the urine dipstick last.

Note: Testing for Chlamydia and Gonorrhea is done at screening and when clinically indicated only.

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 female participant not to clean the labia prior to specimen collection. Male participants should withdraw foreskin if present.
- 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 Dipstick Urinalysis

Dip the urinalysis test strip into an aliquot of urine. 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.

Notify the NL immediately if any kit inventory or quality control problems are identified, so that appropriate action can be taken.

12.5.3 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 urine 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 Fisher Sure-Vue or Quidel QuickVue One-Step hCG urine pregnancy test must be used at all sites. Perform the test according to site SOPs and the package insert. Do not perform any other urine pregnancy tests for confirmatory purposes.

12.5.4 Chlamydia and Gonorrhea Testing

Note: Testing for Chlamydia and Gonorrhea is done at screening and when clinically indicated only.

This testing will be done using the Gen-Probe Aptima or Becton Dickinson ProbeTec NAAT Methods by the local laboratory.

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.
- Results will be sent to the clinic for reporting on the CRF.

12.6 Blood Testing

The blood tests performed depend 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 primary tubes with a SCHARP-provided PTID label at the time of collection.

After collection:

- Allow red top tubes (no additive) to clot, then centrifuge per site SOPs 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 plasma archive.

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

HIV testing must be validated at the study site per the CLIA standards. All tests, and associated QC procedures, must be documented on local laboratory log sheets or other laboratory source documents.

HIV infection status at screening will be assessed using an FDA-approved HIV test per the MTN-007 HIV testing algorithm (see appendix II in the current version of the MTN-007 protocol). If the test is non-reactive, the participant will be considered HIV-seronegative. If the test is reactive, an FDA-approved Western Blot (WB) or Immunofluorescent Antibody (IFA) test will be performed; if additional blood must be drawn for the WB or IFA, this is still considered sample 1 per the algorithm. If the WB or IFA is negative, the participant will be considered HIV-seronegative; this situation is not anticipated. Contact the MTN NL if this occurs. If the WB or IFA is positive, the participant will be considered HIV-seropositive. A second specimen will be drawn for confirmatory testing. If the WB or IFA is indeterminate, the site should contact the NL for further instructions.

Notify the NL immediately if any kit inventory or quality control problems are identified, so that appropriate action can be taken.

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 lab 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; 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 four-fold or revert to seronegative 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-007 Protocol Safety Review Team.

12.6.4 Hepatitis B Surface Antigen and HSV-1 and HSV-2 IgG Serology

This testing will be done on serum per local SOPs

12.6.5 HSV serology

Testing will be done for both HSV-1 and HSV-2 IgG antibody
Testing will be performed on serum per local SOPs

12.6.6 Hematology Testing

Complete blood counts (CBC) 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 per local site SOPs.

12.6.7 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

- BUN
- Creatinine

These chemistry tests will be collected and performed according to local laboratory SOPs.

12.6.8 Plasma Archive

For plasma archive, use EDTA. These will be stored at ≤ -70°C and batched onsite until the MTN-007 study team requests shipping and/or testing. The Pittsburgh site will send whole blood EDTA to be processed at the NL on the day of collection.

- LDMS will be used to label and track the specimens.
- If at room temp, freeze within 4 hours. If refrigerated or on ice after collection, freeze within 24 hours.
- Prepare as many 1.5 mL aliquots as available to store. If less than 1.5 mL of plasma are available, store that plasma and inform the MTN NL for instruction.
- The MTN NL will send instructions to the site when shipping and/or testing is required.

12.7 Testing of Rectal Specimens

The tests performed on rectal specimens depend 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.

Rectal samples should be collected in the following order.

1. Rectal swab for GC/CT
2. Rectal swab for microflora
3. Rectal sponges for cytokines
4. Digital rectal examination
5. Rectal lavage/effluent for epithelial sloughing
6. Stool sample for fecal calprotectin
7. *Flexible sigmoidoscopy and biopsies at 15cm for Histology, Cytokine RT PCR, Mucosal T cell phenotyping, and mucosal gene expression array
8. *Anoscopic biopsies at 9cm for Histology, Cytokine RT PCR, Mucosal T cell phenotyping, and mucosal gene expression array

Table 12-6 gives a brief summary of how these rectal samples should be handled.
**If at anytime the collection of biopsies is limited, submit for assays in order of importance - Histology, Mucosal Gene Expression Array, Cytokine RT PCR, then T Cell Phenotyping.*

Table 12-6
Specimen Handling Guidelines

Assay	Primary Specimen	Additive/Container	Minimum volume required	Handling Requirements
Rectal GC/CT	Rectal Swab	Transport tube	N/A	Store at 2-30°C for up to 30 days
Rectal Microflora	Rectal Swab	Port-A-Cul tube	N/A	Store at RT up to 4 hours, then refrigerate
Rectal Sponge for Cytokines	Rectal Sponge	5mL polystyrene tube	N/A	Freeze at -80°C within 4 hours of collection
Epithelial Sloughing	Lavage Effluent	2% paraformaldehyde	N/A	Process within 8 hours of collection
Fecal Calprotectin	Stool	White container from Genova Kit	20g stool (Lima bean sized)	Store at RT
Histology	Biopsy	10% formalin *(orange top vial)	1 biopsy per site	Store at RT
Cytokine RT PCR	Biopsy	RNA*later* (green top tube)	1 biopsy x2 per site	Store at 4ºC overnight (16-24 hours) then transfer to -80ºC.
Mucosal T Cell Phenotyping	Biopsy	cRPMI in 15ml conical tube	3 biopsies per site	Keep refrigerated
Mucosal Gene Expression Array	Biopsy	RNA*later* (blue top tube)	1 biopsy per site	Store at 4ºC overnight (16-24 hours) then transfer to -80ºC.

**The Magee site will be using cassettes and pre-filled formalin cups.*

12.7.1 Rectal NAAT for Gonorrhea and Chlamydia

Note: Testing for Chlamydia and Gonorrhea is done at screening and when clinically indicated only. Product gel may cause interference during testing. Please be sure gel has not been used within the past 24 hours.

This testing will be done by the local lab using either the BD Probe Tec or Gen-Probe Aptima Methods. Following are collection and transport instructions:
Instructions for collection and transport of rectal swabs for GC/CT testing

- For specimens to be tested with the ProbeTec instrument use the BD ProbeTec CT/GC Endocervical Specimen Collection and Dry Transport kit.
- For specimen to be tested with the Gen-Probe Aptima instrument use the Gen-Probe Aptima Unisex Swab (blue swab).
- Label the transport tube with the participants PTID number and date.
- Remove the swab from the plastic transport tube and insert into the rectum according to the procedure outlined in the SSP for Clinical Considerations (Section 10) and rotate gently through 360 degrees and remove.
- Immediately place the swab in the transport tube, break off shaft of swab and cap. The specimen can now remain at 2-30°C for 30 days.
- Place the transport tube in a biohazard zip-lock bag and transport to the local laboratory for testing.
- Specimens for GC/CT are not logged into LDMS. The results are sent to the clinic and are reported on a CRF.

12.7.2 Rectal microflora

Rectal swabs will be collected for semi-quantitative cultures and sent to the MTN NL. Shipping instructions follow.

- The following supplies will be provided by the NL: Sterile Dacron swabs, Port-a-cul transport tubes, and shipping containers. Sites will need to provide their own ice packs.
- Rectal swabs collection:
    - Insert the swab into the anal canal following the procedure described in the SSP for Clinical Considerations.
    - Rotate the swab through 360 degrees.
    - Slowly remove the swab and place into a Port-A-Cul transport tube (labeled with a SCHARP label), submerging the swab into the gel. Break off the shaft of the swab and cap.
- 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 culture into LDMS (specimen type =REC) and label the Port-A-Cul tube with an LDMS label.
- Use LDMS to generate a shipping manifest for the culture to be shipped.
- Ship the Port-A-Cul tube 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, and a copy of the LDMS manifest in a cardboard box lined with Styrofoam.
- Use diagnostics packing code 650, UN3373.

- The Research Institute is not open for delivery on the weekend. Please ship overnight Monday thru Thursday.

Lorna Rabe
Magee-Womens Research Institute
204 Craft Ave, Room A530
Pittsburgh, PA 15213
Phone# 412-641-6042

Notify the MTN NL via email (lrabe@mwri.magee.edu, kstoner@mwri.magee.edu, pkunjara@mwri.magee.edu) when the shipment has been picked up from the site by the courier/shipping company. Attach an electronic copy of the LDMS batch to the e-mail notification, and include the shipment tracking number.

12.7.3 Rectal Sponge for Cytokines

- The clinician will collect specimen at 9 cm in the rectum according to the procedures outlined in the SSP for Clinical Considerations.
- After collection the sponge will be placed in a 5.0ml polystyrene tube (Nalgene Cryogenic vials cat. No. 5000-0050) containing 50µl PBS and labeled with the PTID, visit #, and date.
- Complete the LDMS tracking sheet and submit to lab for LDMS entry.
- Log into LDMS and label specimen with LDMS label.
- Freeze at -80°C within 4 hours of collection until ready to ship.
- Specimens may be batched and shipped on dry ice. Once the NL notifies the site to ship, use LDMS to create a shipping manifest.
- Ship specimens to MTN NL Pittsburgh Monday through Wednesday for overnight delivery. See section 12.7.2 for shipping address.

12.7.4 Fecal Calprotectin

Genova Diagnostics kits provide the collection container, transport container, shipping box and FedEx labels. The instructions are printed on the outside of each kit and in Appendix 12-2.

- 20 grams of stool collected after the Normasol enema are transferred into the white container provided in the Genova kit and sent to Genova overnight.
- For specimens collected on Friday, store the specimen at ambient temperature (room temperature) and ship on Monday. The specimens must arrive at Genova within 5 days of collection.
- Results will be sent to Dr. Ian McGowan in Pittsburgh.

12.7.5 Epithelial sloughing

The clinic will transport the effluent in a container with a SCHARP label and date to the local laboratory for initial processing. The specimen should be processed within 8 hours of collection. After processing, the specimen will be shipped to the MTN NL the day of collection.

Procedure for processing specimen at the site prior to shipping:

***If the effluent is clear:**

1. Label a 50 cc conical tube and a cryovial with the PTID and date of collection.
2. Transfer the effluent to a 50 cc conical tube.
3. Record the volume of fluid on the LDMS tracking sheet.
4. Centrifuge the fluid at 1000 rpm for 5 minutes.
5. Remove as much supernatant as possible without disturbing the cell pellet and discard.
6. Add 1 mL of 2% paraformaldehyde (See Section Appendix 12-3 for ordering and preparing solution).
7. Resuspend the pellet gently by swirling and transfer to the cryovial.
8. Fill out the LDMS Tracking sheet and submit to lab for LDMS entry.
9. Log the specimen into LDMS, label specimen with LDMS label, and create a shipping manifest.
10. The specimens must be shipped the day of collection with ice packs to the MTN NL. (Send in the same box as the biopsies for mucosal T cell Phenotyping. See section 12.7.2 above for shipping

****If the effluent is muddy with excessive fecal material:**

1. Label **two** 50 cc conical tubes and **two** cryovials with the PTID and date of collection.
2. Transfer the effluent to **one** of the 50 cc conical tubes.
3. Record the volume of fluid on the LDMS tracking sheet.
4. Centrifuge the fluid at 1000 rpm for 5 minutes.
5. Transfer as much supernatant as possible without disturbing the cell pellet into the second 50 cc conical tube and centrifuge as described above.
6. Remove the supernatant from the second conical tube without disturbing the cell pellet and discard. **Note**: After the second centrifugation, you will have two 50 cc conical tubes with a pellet.
7. Add 1 mL of 2% paraformaldehyde to both pellets.
8. Follow steps 7-10 above.

12.7.6 Biopsy for Histology

- There will be biopsies from the 9 cm and the 15 cm sites. Label 2 containers with the PTID, visit #, visit date, and site location (9 cm and 15 cm).
- The clinic staff will place 1 biopsy from each site into the designated container with 10% formalin. The Pitt site will place biopsies into histology cassettes and pre-filled containers of 10% formalin which will be delivered to MWRI. UAB and Fenway sites will place biopsies into microtubes filled with 10% formalin for shipping. These can be kept at room temperature.
- Complete the LDMS tracking sheet and submit to lab for LDMS entry.
- The tissue processing, staining and evaluation will be performed at the MTN NL.
- Log specimens into LDMS, label specimen with LDMS label, and create a shipping manifest.
- Ship the specimens to the MTN NL at room temperature or on ice with the other samples within 24 hours. See section 12.7.2 above for shipping instructions.

12.7.7 Biopsies for Cytokine RT PCR

- There will be 2 biopsies from the 9 cm site and 2 biopsies from the 15 cm site. Label 4 green topped (Nalgene 5045-0004) cryovials (Nalgene 5000-0020) with the PTID, visit #, visit date, and biopsy site (9 cm or 15 cm).
- Submerge 1 tissue biopsy from each site into the appropriate cryovial containing 1.5 mL of RNA*later* Solution (Ambion, Invitrogen Cat #AM7020) See Section Appendix 12-3 below.
- Store each vial containing one rectal biopsy in RNA*later* at 4ºC overnight (16-24 hours).
- Complete the LDMS tracking sheet and submit to lab for LDMS entry.
- Log the specimens into LDMS and label specimens with LDMS label.
- Transfer vials from 4ºC to -80ºC. Each biopsy must be stored a minimum of 24 hours at -80ºC prior to shipping.
- Batch and send to MTN NL. You will be notified when to send the specimens. See section 12.7.2 for shipping address and e-mail notification.

12.7.8 Biopsies for Mucosal T Cell Phenotyping

- There will be biopsies from the 9 cm and 15 cm sites. Label two 15 cc conical tubes with the PTID, visit #, visit date, and site location (9 cm or 15 cm).
- Submerge 3 biopsies from each site into the site designated tube containing 12-15 mL of cRPMI media (See Appendix 12-3 for ordering and preparing media).
- Keep refrigerated.
- Complete the LDMS tracking sheet and submit to lab for LDMS entry.
- Log the specimen into LDMS, label specimen with LDMS label, and create a shipping manifest.
- Send overnight the day of collection to MTN NL with ice pack. See section 12.7.2 for shipping and e-mail notification.

12.7.9 Mucosal Gene Expression Array

- Take two blue topped (Nalgene 5045-0003) cryovials (Nalgene 5000-0020) each containing 1.5 mL of RNA*later* (Ambion, Invitrogen Cat #AM7020) and label them with PID, study visit, biopsy site, and date.
- Place one biopsy from each sampling site (anoscopy at 9 cm and Flex. Sigmoidoscopy at 15 cm) into each cryovial and submerge the tissue in the RNA*later* solution.
- Store each vial containing one rectal biopsy in RNA*later* at 4ºC overnight (16-24 hours).
- Complete the LDMS tracking sheet and submit to lab for LDMS entry.
- Log the specimen into LDMS and label specimen with LDMS label.
- Transfer vials from 4ºC to -80ºC. Each biopsy must be stored a minimum of 24 hours at -80ºC prior to shipping.
- When a batch of 20-30 vials has been collected, ship samples on dry ice Monday thru Wednesday to:

  MTN Immunology Core
  Attn: Florian Hladik, MD, PhD
  Fred Hutchinson Cancer Research Center
  1100 Fairview Avenue North, D3-355
  Seattle, Washington 98109-1024

- Generate a manifest (excel, preferably) to include shipper's address & phone number, recipient's address & phone number, and identification of each sample in the shipment. This can be generated using the LDMS Shipment Module. When creating the batch, select Excel as the shipment type located in the top right corner of the View Shipment screen.
- Send a pre-notification email to the McElrath Lab Repository:
    - Jen Leo (jleo@fhcrc.org)
    - Leo French (lfrench@fhcrc.org)
    - Kristina Robinson (ksrobins@fhcrc.org).
- The pre-notification email must include the manifest as an attachment and the FedEx tracking number for the shipment. The Repository will send an email to the shipper the day the shipment arrives, indicating receipt of shipment.
- Also, shipments are only sent Monday thru Wednesday. Exceptions should be cleared with the lab on a case-by-case basis to make sure someone is available to receive the shipment.

Appendix 12-1

MTN 007

LDMS Specimen Tracking Sheet

For login of MTN 007 stored specimens into LDMS

Participant ID	Visit Code	Specimen Collection Date
☐☐☐ - ☐☐☐☐☐ - ☐	☐.☐	☐☐ ☐☐☐ ☐☐
Site Number / Participant Number / Chk		*dd* / *MMM* / *yy*

# of TUBES or SPECIMENS	PRIMARY SPECIMEN	PRIMARY ADDITIVE	ALIQUOT DERIVATIVE	ALIQUOT SUB ADDITIVE/ DERIVATIVE	INSTRUCTIONS FOR PROCESSING LAB
☐	Blood – *Plasma* **(BLD)**	**EDT** (purple top)	**PL1**	**N/A**	Store in aliquots of 1-2 ml. If held at room temperature, plasma must be frozen within 4 hours of collection. If refrigerated or on ice, plasma must be frozen within 24 hours of collection.
☐	Rectal Swab – *Microflora* **(REC)**	**NON** (no additive)	**SWB**	**N/A**	Ship to NL on ice the day of collection
☐	Rectal Sponge – *Cytokines* **(REC)**	**PBS** (phosphate buffered saline)	**SPG**	**N/A**	Store @ <-70°C within 4 hours of collection.
☐	Rectal Effluent – *Epithelial Sloughing* **(REC)**	**NOR**	**LAV**	**PFM**	Process and ship to NL the day of collection. Ship on ice. **Volume collected**: _____ mL
☐	Anoscopy Biopsies - *Histology* **(ARB)**	**FOR**	**TIS**	**N/A**	Ship to NL at room temperature the day of collection.
☐	Anoscopy Biopsies - *Cytokines* **(ARB)**	**RNL**	**TIS**	**N/A**	Store @ 4°C overnight then transfer to -80°C. Must be stored at -80°C for a minimum of 24 hours prior to shipping. Specify cytokine test in specimen management. (See lab SSP section Table 12-4)

Comments: _____

_____

Initials: _____ (Sending Staff) _____ (Receiving Staff) **LDMS Data Entry Date:** ☐☐ ☐☐☐ ☐☐ (*dd* / *MMM* / *yy*) / _____ (LDMS Staff)

Version 2.0, 01-NOV-10

MTN 007 **LDMS Specimen Tracking Sheet**

For login of MTN 007 stored specimens into LDMS

MTN 007 LDMS Specimen Tracking Sheet (non-DataFax) Page 1 of 2

Purpose: This non-DataFax form is used to document collection and entry of MTN 007 specimens into the Laboratory Data Management System (LDMS).

General Information/Instructions: A copy of this form accompanies specimens for storage (in their original specimen collection containers) to the 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. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Item-specific Instructions:

- **Visit Code:** Record the visit code of the visit at which the LMDS specimens were collected.
- **# of TUBES or SPECIMENS COLLECTED**: In the box provided, record the total number of tubes or specimens collected for that primary specimen type. 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 Data Entry Date – LDMS Staff:** The LDMS laboratory staff person who entered the specimens into LDMS, records his/her initials here.

Version 2.0, 01-NOV-10

MTN 007

LDMS Specimen Tracking Sheet

For login of MTN 007 stored specimens into LDMS

Participant ID	Visit Code	Specimen Collection Date
☐☐☐ - ☐☐☐☐☐ - ☐	☐.☐	☐☐ ☐☐☐ ☐☐
Site Number / Participant Number / Chk		*dd* / *MMM* / *yy*

# of TUBES or SPECIMENS	PRIMARY SPECIMEN	PRIMARY ADDITIVE	ALIQUOT DERIVATIVE	ALIQUOT SUB ADDITIVE/ DERIVATIVE	INSTRUCTIONS FOR PROCESSING LAB
☐	Anoscopy Biopsies - *Phenotyping* **(ARB)**	**RPM**	**TIS**	**N/A**	Ship to NL on ice the day of collection
☐	Anoscopy Biopsies - *Gene expression microarrays* **(ARB)**	**RNL**	**TIS**	**N/A**	Store @ 4°C overnight then transfer to -80°C. Must be stored at -80°C for a minimum of 24 hours prior to shipping. Specify Gene expression test in specimen management. (See lab SSP section Table 12-4)
☐	Sigmoidoscopy Biopsies - *Histology* **(FSR)**	**FOR**	**TIS**	**N/A**	Ship to NL the day of collection.
☐	Sigmoidoscopy Biopsies - *Cytokines* **(FSR)**	**RNL**	**TIS**	**N/A**	Store @ 4°C overnight then transfer to -80°C. Must be stored at -80°C for a minimum of 24 hours prior to shipping. Specify cytokine test in specimen management. (See lab SSP section Table 12-4)
☐	Sigmoidoscopy Biopsies - *Phenotyping* **(FSR)**	**RPM**	**TIS**	**N/A**	Ship to NL on ice the day of collection
☐	Sigmoidoscopy Biopsies - *Gene expression microarrays* **(FSR)**	**RNL**	**TIS**	**N/A**	Store @ 4°C overnight then transfer to -80°C. Must be stored at -80°C for a minimum of 24 hours prior to shipping. Specify Gene expression test in specimen management. (See lab SSP section Table 12-4)

Comments: _____

Initials: _____ (Sending Staff) _____ (Receiving Staff) **LDMS Data Entry Date:** ☐☐ (*dd*) ☐☐☐ (*MMM*) ☐☐ (*yy*) / _____ (LDMS Staff)

Version 2.0, 01-NOV-10

MTN 007 **LDMS Specimen Tracking Sheet**

For login of MTN 007 stored specimens into LDMS

MTN 007 LDMS Specimen Tracking Sheet (non-DataFax) Page 2 of 2

Item-specific Instructions:

- **Visit Code:** Check to make sure the Visit Code recorded on page 1 and page 2 match.
- **NUMBER OF TUBES or SPECIMENS COLLECTED**: In the box provided, record the total number of tubes or specimens collected for that primary specimen type. 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 Data Entry Date – LDMS Staff:** The LDMS laboratory staff person who entered the specimens into LDMS, records his/her initials here.

Version 2.0, 01-NOV-10

Appendix 12-2
Collection and Transport of Rectal Lavage Specimens for Fecal Calprotectin Test

Background

Calprotectin is a calcium-binding protein secreted predominantly by neutrophils; it constitutes approximately 60% of their cytosolic protein. Elevated fecal calprotectin levels have been observed in patients with inflammatory bowel disease (IBD) and GI tract infections. Fecal calprotectin correlates strongly with ^{111}indium-labeled granulocytes, as well as IBD activity determined by histological and endoscopic evaluation. Elevated levels have been observed to precede clinical relapse in patients with quiescent IBD. Fecal calprotectin is also elevated in patients with non-steroidal anti-inflammatory drug (NSAID)-induced enteropathy.

Rectal Lavage is a procedure which involves instilling a solution to wash the rectum. The effluent is collected for analyses.

Specimen

Patient Preparation: See procedure steps below

Type: Random stool

Optimum/Minimum Specimen volume: 20 grams of stool, in stool cup.

Handling Instructions:
Samples may be stored at ambient temperature for up to 5 days or stored frozen at -20^{0}C for up to one year.

Ship the specimen overnight in the pre-paid mailing envelope supplied by the Genova kit. (See SOP for shipping biological specimens) The specimen should be packaged according to IATA regulations regarding shipment of biological material.

Unacceptable Specimens: Sample ambient longer than 5 days

Materials

Pre-packaged enema to be used for lavage (Abbott Labs, Normosol-R, 500ml #00409796703)
Enema bottle, 120 mL (MediDose, #EPS212316)
Genova Diagnostics Calprotectin kit (#64) including specimen pan
60ml catheter tip syringe (BD #309-620)
50ml conical tubes (Corning #430828)
PRE Personal lubricant (provided by MTN)

Procedure –Stepwise

Clinical Staff:

1. Place specimen pan into available toilet.
2. Fill enema bottle with 120 mL of appropriate solution, if not pre-packaged.
3. Have subject rotate onto his/her left-hand side with right knee bent.
4. If enema bottle is not pre-lubricated, apply a dime size amount of water-based lubricant (PRE Personal lubricant provided by MTN. DO NOT USE Surgilube and other chlorhexidine containing lubricants!)
5. Gently insert the tip of the enema bottle into the rectum.
6. Slowly instill the solution into the rectum.
7. After holding the fluid in the rectum for approximately 5 minutes ask the subject to use the restroom, taking care to relieve themselves into the specimen pan.
8. Transfer stool with the flat wooden stick provided in the kit into the white-top vial that includes the participant I.D.# and collection date on it.
9. Add a sufficient stool to fill to the 20 mL line, ~ ½ inch.
10. Recap white-top vial securely.
11. Place white-top vial (with specimen) in the biohazard bag and seal.
12. Fill out the requisition to include the fields listed below. See example. Diagnosis code and physician signature are not required.
    a. Collection Date
    b. Test Ordered: Calprotectin
    c. Last name: Visit Code
    d. First name: PID
    e. Payment/Billing Option: Bill Practitioner Account
13. Transport the white-top vial in Biohazard bag to the laboratory for immediate shipping.

Laboratory Staff:

1. Place biohazard bag that contains specimen, into small cardboard box provided in kit. **** Specimen MUST be returned in this bag & box.****
2. Write your name and address on the "From" portion of the FedEx mailer. Keep shipping and tracking numbers for tracking purposes.
3. Place these items in the pre-paid mailing envelope:
    - Cardboard box containing Biohazard bag with the specimen in the white-top vial.
    - Completed Requisition, refolded with personal information hidden.
4. Schedule a pickup:
    - Call 1-800-GoFedEx (1-800-463-3339)
    - Say, "Return a package."
    - When connected with a FedEx customer service representative, please tell them:
        - ❖ We are using FedEx Express Billable Stamps.
        - ❖ Your name, phone number, address, and zip code.

- FedEx will ask for the number of packages and then provide you with your pickup time.

**** For specimens received on a Friday, ship out Monday morning****

Methodology: Enzyme-linked Immunosorbent Assay (ELISA)

Reference Range*: < 50 μg Calprotectin/g stool Normal
50-100 μg Calprotectin/g stool Moderate GI inflammation
> 100 μg Calprotectin/g stool Significant GI inflammation
> 250 μg Calprotectin/g stool Mild to moderate IBD activity
> 500 μg Calprotectin/g stool Severe IBD activity

*Elevated calprotectin levels have been reported in healthy infant's ≤10 weeks of age.

Genova Diagnostics®
Innovative Testing for Optimal Health

63 Zillicoa Street
Asheville, NC 28801
888.540.2199
www.GenovaDX.n

COLLECTION DATE →

Date Final Sample Collected:
Mo. Day Year

Requisition

***This form must be completed** (including responsible party signature) and returned with the specimen in order to process this test.*

Check all requested tests below and provide Diagnosis Codes for each test. Individual Diagnosis Codes are required for Medicare and Insurance billing.

Test Ordered: ____ **Pancreatic Elastase (PE)**

	CPT	Diagnosis Code (Required)
Pancreatic Elastase	82656	

And/Or

Test Ordered: X **Calprotectin**

	CPT	Diagnosis Code (Required)
Calprotectin	83993	NOT REQUIRED

Physician Information

☐ *Address change? Check here and indicate new address on reverse side.*

ID# X00RB
Ian McGowan, MD
MTN Lab- Lab B530 F/G
204 Craft Ave
Pittsburgh, PA 15213
412-641-8905

Physician Signature *(Required)*

Print _____

Sign _____

NPI# _____

- ***Medicare and Medicaid will not reimburse for tests which are ordered for screening purposes only. Physicians are legally responsible for limiting requests for tests to only those that are medically necessary for the diagnosis and treatment of the patient. Your ordering of the test(s) means that you believe the test(s) is medically necessary***
- *If the ordering physician is different from the preprinted physician above, please ensure your name, address, and NPI# or Tax ID# is provided.*

} NOT REQUIRED

THIS SPACE FOR LAB USE ONLY

1697963

Patient Information

VISIT CODE → VST 2 ; PID → 12345789

Social Security #: - - Gender: M F

Name (last): VST 2 (first): 12345789 (middle):

Date of Birth: - - Age: Phone:

Mailing Address:

City: State: Zip: -

Country: Email:

Responsible Party Information: *(if different from patient)*

Name (last): (first): (middle):

Mailing Address:

City: State: Zip: -

Phone: Social Security #: - -

Payment/Billing Options

(select one):

☑ Bill Practitioner Account
If nothing is indicated, practitioner account will be billed.

☐ Bill Insurance

☐ Bill Medicare

☐ Payment Enclosed
Contact your health care practitioner for pricing.

Payment provided:
$ _____

Check or Credit Card Information

Medicare, Medicaid patients: see reverse side for Important Information. Please do not send cash. Contact your health care practitioner for pricing. A receipt will be provided which can be used to file your own insurance claim.

Credit Card from:
☐ Patient
☐ Physician

Select one:
☐ MasterCard ☐ Visa
☐ Discover ☐ AMEX

Credit Card #:
Expiration Date: ____/____
Cardholder Signature: _____
Printed Name: _____
Billing Address: _____
_____
City: _____ State: ___ Zip: _____

Check from: ☐ Patient ☐ Physician Check #: _____
(make checks payable in US dollars to Genova Diagnostics)

Insurance Information

(Print clearly) ***Medicare, Medicaid patients: see reverse side for Important Information.*** *Fill out this section only if* you intend for Genova Diagnostics to file a claim on your behalf. Contact your health care practitioner for pricing. Genova Diagnostics does not participate in any HMO or other managed care contracts, so out-of-network benefits may apply. It is your responsibility to verify insurance coverage; Genova Diagnostics does not guarantee insurance coverage. Please call your insurance company for preauthorization, referral, and/or benefit verification, referring to the CPT code(s) listed by profile ordered on the requisition. Attach a copy of both sides of your insurance card to this form.

	Primary	**Secondary**
Insurance Company:		
Claims Address:		
City/State/Zip:		
Phone #:	( )	( )
Subscriber Name:		
Subscriber ID #/Medicare #:		
Group #:		
Subscriber Date of Birth:	/ /	/ /
Relation to Patient:	☐ Self ☐ Spouse ☐ Other	☐ Self ☐ Spouse ☐ Other

Except in the case of prepayment, I authorize payment of all medical benefits to be paid directly to Genova Diagnostics and authorize the release of any medical information necessary for this insurance claim. I permit a copy of this requisition to be used in place of the original. The patient/ responsible party is personally & fully responsible for payment of any balance not paid by their insurance within 45 days of billing. This excludes government carriers such as Medicare, Tricare.

Patient/Responsible Party Signature *(required)* X _____

Appendix 12-3
Procedure for preparing reagents for MTN-007

Equipment:

1. 2-8°C Refrigerator
2. -20°C freezer
3. Biological laminar flow hood
4. Pipette Aid

Disposables:

1. Corning 15 cc conical tubes (#430766)
2. 10 mL serological pipettes
3. 25 mL serological pipettes

Reagents:

1. RPMI (1x) 1640 w/HEPES w/L-glutamine Invitrogen #22400-089 (500 mL) Freeze until needed.
2. Heat inactivated, certified Fetal Bovine Serum (FBS), Invitrogen #10082-147 (500 mL) or 10082-139 (100 mL). Aliquot into 50 cc tubes and freeze at -20^{o}C
3. Antibiotic/antimycotic (100x)Invitrogen #15240-104 (100 mL) aliquot 5 mL quantities into 10 mL size tubes and freeze at -20^{o}C

Procedure:

1. Complete RPMI media (for transporting biopsies for T cell phenotyping)

Ingredients	Quantities for 500 mL	100 mL
RPMI	445 mL	94 mL
FBS (f.c. 10%)	50 mL	10 mL
Antibiotics (f.c. 1%)	5 mL	1 mL

1. Take precautions to maintain the sterility of the media and use sterile techniques with transferring.
2. Thaw the RPMI, FBS, and antibiotic/antimycotics.
3. Combine the above ingredients and mix
4. Dispense 10-12 mL aliquots into 15 cc tubes labeled cRPMI and expiration date of 1 month from preparation.
5. Store at 4^{o}C

2. Paraformaldehyde solution, 2% in PBS (for transporting cells for epithelial sloughing)

Order from USB, Paraformaldehyde solution 4%, item #19943, 1 liter

1. Dilute the 4% solution to 2% in PBS.
2. Dispense 1 mL aliquots into cryovials.
3. Store at 4^{o}C until used.

3. RNA*later* (to be used for collecting biopsies for cytokine RT-PCR and biopsies for Mucosal Gene Expression Array)

Order RNA*later* Solution (Ambion, Invitrogen Cat #AM7020) 100 mL

1. Dispense 1.5 mL aliquots of the RNA*later* into cryovials.
2. Store at room temperature until used.

Section 13. Data Collection

This section provides information needed to successfully complete and submit MTN-007 case report forms (CRFs). It is important for sites to collect and record data carefully on CRFs; by doing so, the Statistical and Data Management Center (SDMC) can be confident that the data they are analyzing are accurate and complete. For questions about this section or about general data collection policies, procedures, or materials, please contact Missy Cianciola (missy@scharp.org).

For this study, the SDMC is SCHARP (the Statistical Center for HIV/AIDS Research and Prevention). SCHARP is located in Seattle, WA, USA, and is in the US Pacific Time (PT) time zone. The SCHARP MTN-007 team members, along with their job roles and e-mail addresses, are listed below.

Role on MTN-007	Name	E-mail Address
Protocol Statistician	James Dai	jdai@scharp.org
Statistical Research Associates	Marla Husnik, Jason Pan	marla@scharp.org; zpan@scharp.org
Project Manager	Missy Cianciola	missy@scharp.org
Clinical Affairs Safety Associate	Yevgeny Grigoriev	ygrigori@scharp.org
Protocol Programmer	Katie Weaver	kweaver@scharp.org
Reports Programmer	Kate Bader	kate@scharp.org
Laboratory Programmer	Laura Robins-Morris	lrobins@scharp.org
CASI Programmer	Lynda McVarish	lmcv@scharp.org
Data Coordinator	Susan Tracy-Waisanen	stracy@scharp.org
Technical Document Specialist	Stacie Kentop	stacie@scharp.org

13.1 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 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" each CRF into the study database using Intelligent Character Recognition.
- Each CRF is then 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 re-fax 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.

13.2 DataFax Form Completion

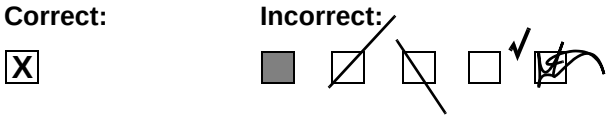
13.2.1 General Guidelines

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 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 the 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 CRFs 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.

13.2.2 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.



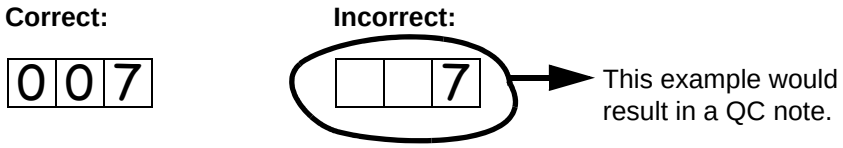
Mark only one response box for each item unless the "Mark all that apply" instruction is present.

13.2.3 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 boxes with leading 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:

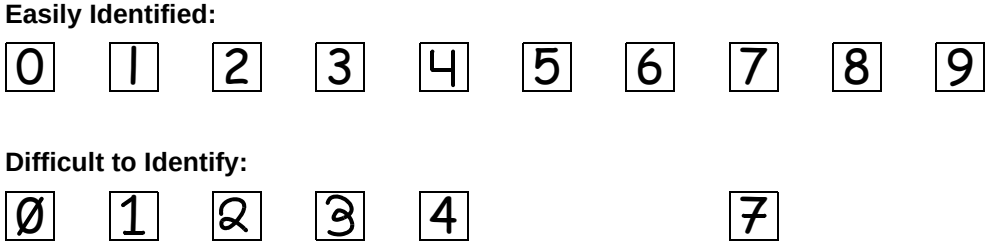


- Write the number(s) as large as possible while staying within the boundaries of the box; try not to stray outside the boundaries of the box.

  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:

- 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.



13.2.4 How to Record Dates

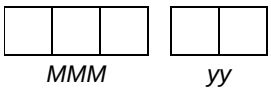
Dates are recorded using the "dd-MMM-yy" format, where "dd" represents the two-digit day, "MMM" represents the three-letter abbreviation of the month (in capital letters), and "yy" represents the last two digits of the year.

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:

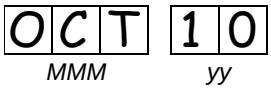
Month	Abbreviation	Month	Abbreviation
January	**JAN**	July	**JUL**
February	**FEB**	August	**AUG**
March	**MAR**	September	**SEP**
April	**APR**	October	**OCT**
May	**MAY**	November	**NOV**
June	**JUN**	December	**DEC**

For example, November 8, 2010 is recorded as:

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:

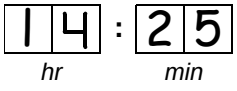


A diagnosis date of October, 2010 would be recorded as follows:



13.2.5 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:



Midnight is recorded as 00:00, not 24:00.

The following chart shows equivalencies between the 12- and 24-hour clocks. Please note that 12:00am is often referred to as “midnight” and 12:00pm is often referred to as “noon”.

12-hour clock (a.m.)	24-hour clock
Midnight	00:00
1:00 a.m.	01:00
2:00 a.m.	02:00
3:00 a.m.	03:00
4:00 a.m.	04:00
5:00 a.m.	05:00
6:00 a.m.	06:00
7:00 a.m.	07:00
8:00 a.m.	08:00
9:00 a.m.	09:00
10:00 a.m.	10:00
11:00 a.m.	11:00

12-hour clock (p.m.)	24-hour clock
Noon	12:00
1:00 p.m.	13:00
2:00 p.m.	14:00
3:00 p.m.	15:00
4:00 p.m.	16:00
5:00 p.m.	17:00
6:00 p.m.	18:00
7:00 p.m.	19:00
8:00 p.m.	20:00
9:00 p.m.	21:00
10:00 p.m.	22:00
11:00 p.m.	23:00

13.2.6 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.

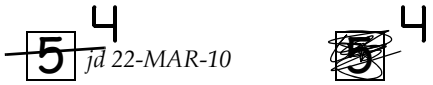
Note: Never write over an entry once it is recorded. Use the standards outlined in the following paragraphs when changing, clarifying, or amending data.

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 un-readable with multiple cross-outs),

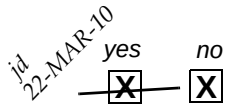
- place the correct or clarified answer near the box, and initial and date the correction near the incorrect entry, as shown below:

Correct: **Incorrect:**



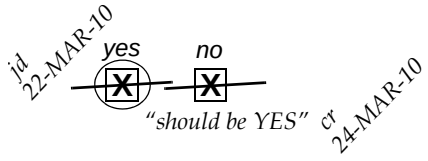
If an **X** is marked in the wrong response box, correct it by doing the following:

- 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:



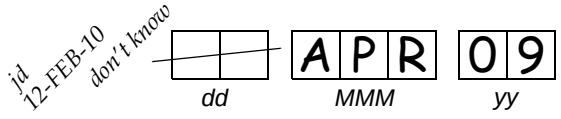
Please note that it is helpful to write in the actual answer (e.g. "should be yes") on the CRF when multiple corrections to one item have been made.

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.

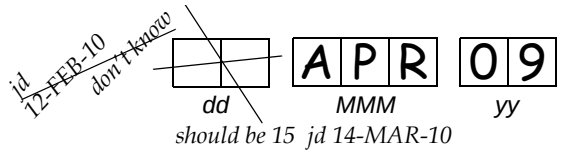
13.2.7 How to Handle Missing and Unknown Data

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:



If an answer is *no longer unknown*, line through any previously lined through boxes (using a diagonal line) and update the form with the new response, 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.

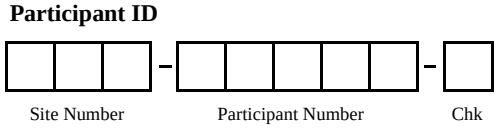
13.3 MTN-007 Study-Specific Data Collection Information

13.3.1 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, in the form of a PTID-Name Link Log. Site staff are responsible for maintaining the log linking PTIDs to participant names (PTID-Name Link log) in accordance with Section 3 of this manual.

The site should assign one PTID to each participant who consented to be screened for the study. Ideally, the PTIDs are assigned in sequential order as participants present for the Screening Visit. The site should ensure that each PTID is assigned only once. Once a participant has received a PTID, he/she will maintain that same PTID throughout the entire study.

PTID boxes are located near the upper left corner of each CRF page. The PTIDs used for this study are nine digits long and are formatted as "XXX-YYYYY-Z." The three parts of the PTID are: 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-007.



13.3.2 Study Visit Timing

Screening and Enrollment

The Screening Visit is defined as the day the participant provides written informed consent to be screened for the study. If necessary, multiple visits may be conducted to complete all required screening procedures. For participants who do not meet the eligibility criteria, the current screening process/attempt will be discontinued once ineligibility is determined.

If a participant later re-screens (starts another screening attempt), **all** screening procedures (except PTID assignment), evaluations, and forms must be repeated, including provision of written informed consent. Once a PTID is assigned to a participant, the same PTID is used for that participant for the entire duration

of the study. If a participant re-screens, only case report forms from the successful Screening and Enrollment visits are faxed to SCHARP DataFax.

The Enrollment Visit must take place no later than 36 days after the Screening Visit. For MTN-007, a participant is considered enrolled once the participant has been assigned an MTN-007 Clinic Randomization Envelope. Assignment of MTN-007 randomization envelopes will be documented using the MTN-007 Clinic Randomization Envelope Tracking Record provided to each site by SCHARP.

Follow-Up Visits

Participants enrolled in MTN-007 are required to complete 5 follow-up visits: 3 clinic follow-up visits and 2 follow-up phone calls. The visit type, visit code, target visit day or range, and visit windows for required MTN-007 follow-up visit are listed in table 13-1.

Table 13-1: List of MTN-007 Target Visit Days/Ranges, and Visit Windows

All windows are listed in days, with Enrollment = Day 0

Visit Type	Visit Code	Visit Window Opens	Target Day/Range	Visit Window Closes
Screening	1.0	Day -36	N/A	Day -1
Enrollment	2.0		Day 0	36 days after Screening
Treatment 1 Visit	3.0	7	Between 7-28 Days after Enrollment	28
Follow-up Phone Call	4.0	8	Within 1 day (24 hours) of Treatment 1 Visit	29
Treatment 2 Visit	5.0	14	At least 7 days after Treatment 1 Visit	42
Final Clinic Visit	6.0	21	The day after the last dose of study product	63
Follow-up Phone Assessment/ Termination Visit	7.0	28	Between 7-14 days after Final Clinic Visit	77

Target Days/Ranges and Visit Windows

Note: *for the purposes of this section, phone calls will be considered follow-up visits, even though an in-person visit is not required for follow-up phone calls.*

In general, the target day/range for the follow-up visits is based on the day the previous visit was completed. The Treatment 1 Visit is targeted to occur 7-28 days after the Enrollment Visit, the Follow-up Phone Call is targeted to occur 24 hours after the Treatment 1 Visit, the Treatment 2 Visit is targeted to occur at least 7 days after the Treatment 1 Visit and the Follow-up Phone Assessment/Termination Visit is targeted to occur 7-14 days after the Final Clinic Visit. study

The Final Clinic Visit is targeted to occur the day after the last dose of product is used by the participant. If the participant starts the 7-day dose of study product the day of the Treatment 2 Visit, the Final Clinic Visit should occur 7 days after the Treatment 2 Visit (the day after the last dose of the 7-day product was taken). Likewise, if the participant starts the 7-day dose of product 14 days after the Treatment 2 Visit, the Final Clinic Visit should occur 21 days after the Treatment 2 Visit (again, the day after the last dose of product was taken). Site staff should be in close contact with the participant in order to determine when

the participant started the 7-day dose of product and, therefore, when the last dose of product will be taken in order to schedule the Final Clinic Visit on the target day.

MTN-007 visit windows are set based on the date of Enrollment and do not change based on when follow-up visits are completed. The visit windows indicate when visits are allowed to be completed, while the target day/ranges indicate when the visit should be completed. For example, the visit window for the Follow-up Phone Call is Day 8 to Day 29. If a participant completes his Treatment 1 Visit on Day 15, the Follow-up Phone Call should be completed on Day 16 (even though the window is broader).

SCHARP will provide sites with an Excel spreadsheet tool that may be used to generate individual participant follow-up visit calendars. The spreadsheet requires that study staff enter the participant's enrollment date, the date some study visits are completed, and the date the participant starts the 7-day dose of product use. Once a visit completion date is entered, the target day/range for the participant's next follow-up visit will be calculated and will appear in the spreadsheet.

Split Visits

In cases where a participant is not able to complete all required visit evaluations on the same day, the participant may return and complete the remaining evaluations on another day, as long as the evaluations are completed within the visit window (ideally within the target range) for the visit. Sites should prioritize rectal specimen collection and AE assessment in cases where all visit procedures cannot be completed on the same day. For example, if a participant lets you know at the beginning of his Final Clinic Visit that he has to leave in one hour, the rectal exam and rectal specimen collection procedures should be prioritized for completion before the participant leaves. The participant may return anytime before the visit window closes to complete the rest of the visit. Visit code assignment for split visits is covered in Section 13.3.3.

Missed Visits

In cases where a participant is not able to complete any part of a required follow-up visit within the visit window, the visit is considered missed. For example, if a participant is unable to be reached by telephone for the Follow-up Phone Call within 24 hours after the Treatment 1 Visit, the Follow-up Phone Call is considered missed. This missed visit is documented by completion of a Missed Visit case report form. In this example, the site should still continue to contact the participant to follow-up on any AEs that may have occurred after the Treatment 1 Visit. If the Treatment 1 Visit or the Final Clinic Visit is missed the site should contact the PSRT.

Interim Visits

A clinic visit is considered an Interim Visit when a participant comes to the site for reasons *other* than to complete regularly scheduled (required) study visit procedures. Interim visits may be performed at any time during the study for reasons that may be administrative (a participant has study-related questions for the staff), product-related (a participant needs additional study product), lab-related (a participant needs a lab test repeated for confirmation), or clinical (a participant needs additional clinical follow-up for an Adverse Event, AE). If any data are required to be reported on a DataFax CRF as a result of an interim contact/visit, an Interim Visit CRF must be completed and faxed to SCHARP DataFax. If no DataFax forms are required for the interim visit (for example, the participant comes to the clinic to obtain more condoms), the interim visit may be documented by a chart note only (no CRFs required).

For example, a participant completes all required evaluations for her Treatment 2 Visit on study Day 36. She returns to the clinic three days later after noticing redness and irritation near the area of the rectum where gel is inserted. Additional follow-up is performed to assess the newly-reported redness and irritation. Since the participant is still within the Treatment 2 Visit window and has already completed all required Treatment 2 evaluations, her visit on day 39 is considered an Interim Visit and an Interim Visit CRF is completed to document the visit. Visit code assignment for interim visits is covered in Section 13.3.3.

Phone contact with a participant is also considered an Interim Visit if 1) the phone contact results in the reporting of a new AE, or 2) during the phone contact, the participant is instructed by site staff to hold or permanently discontinue product use. For example, a site is unable to contact a participant for the Follow-up Phone Call 24 hours after her Treatment 1 Visit. The Follow-up Phone Call is considered missed. However, two days later, the site does get a hold of the participant by telephone and she reports a new symptom, which results in the reporting of a new AE. The phone contact where the new symptom is reported is considered an Interim Visit.

For questions about phone contacts and assignment of visit codes to such contacts, please contact the SCHARP MTN 007 Project Manager.

13.3.3 Visit Codes and Page Numbers

Visit Codes

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 Demographics case report form or the Enrollment case report form), the visit code will be automatically assigned in DataFax.

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. For multiple-paged CRFs, site staff need to make sure that all the pages of the CRF are marked with the same visit code for a given participant and visit.

The following table lists the visit codes assigned to each study visit.

Table 14-2: Visit Code Assignments for Study Visits

Visit Type	Visit Code
Screening Visit	1.0
Enrollment Visit	2.0
Treatment 1 Visit	3.0
Follow-up Phone Call	4.0
Treatment 2 Visit	5.0
Final Clinic Visit	6.0
Follow-up Phone Assessment/Termination Visit	7.0

Visit Codes for Split Visits

When split visits occur, case report forms completed for the visit are all assigned the same visit code (even though some forms and evaluations will have different visit dates). For example, a participant comes to the study clinic for his Final Clinic Visit on day 43. He can only stay at the clinic for an hour, but returns the next day to complete all remaining visit procedures. All case report forms completed on Day 43 and 44 are assigned visit code 6.0 since both of these days are within the 6.0 visit window.

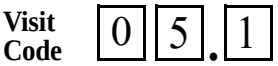
Visit codes for Interim Visits

Interim visit codes are assigned using the guidelines listed below.

- In the boxes to the left of the decimal point, record the two-digit visit code for the most recent scheduled visit (regardless of 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: A participant returns to the site clinic two days after her Treatment 2 Visit requesting additional study product to replace the study product that she lost. She is given additional study product to last until the Final Clinic Visit. The visit is considered an interim visit and is assigned the interim visit code below.

Visit Code for this Interim Visit:



NOTE: *not all interim visits are assigned interim visit codes. An interim visit should be assigned an interim visit code only if data collected at the visit warrants completion of a new DataFax form, such as an AE Log or Product Hold/Discontinuation (PH) Log form. An Interim Visit form must be completed for each and every visit that is assigned an interim visit code.*

Page numbers

Other CRFs, such as log forms (e.g., Adverse Experience Log, Product Hold/Discontinuation Log, Pre-existing Conditions), include boxes in the upper right corner for recording page numbers, as shown below.

Assign page numbers in sequential order, starting with 01 (or 001, for Adverse Experience Log CRFs). For example, the second Concomitant Medications Log page would be assigned page number 02, the third page would be assigned 03, and so on.

13.3.4 Staff Initials/Date

Most CRFs include a line in the lower-right corner for a staff member to write his/her initials and record the date when 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 completing the form. This individual will complete 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.

13.3.5 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 case report forms are required to be completed at each

visit, while other forms are required only at one visit or only when specifically indicated. Table 13-3 lists the DataFax and non-DataFax forms that are **required** to be completed at each MTN-007 study visit.

Table 13-3: MTN-007 Case Report Form Completion Schedule

Screening Visit (Enrollment Day -36)		**VISIT CODE: 1.0**
Form Acronym	**Form Name**	**Plate #**
	REQUIRED	
DEM	Demographics	001
SC	Screening Consent	005
RE	Rectal Exam	041
STI	STI Laboratory Results	131
LR	Laboratory Results	151-152
CM	Concomitant Medications Log	423
Non-DataFax	Screening Visit Eligibility	N/A
Non-DataFax	Medical Eligibility	N/A
Non-DataFax	Participant-Reported Baseline Medical and Menstrual History	N/A
Non-DataFax	Physical Exam	N/A
	AS NEEDED	
HTR	HIV Test Results	351
Enrollment Visit (Day 0)		**VISIT CODE: 2.0**
Form Acronym	**Form Name**	**Plate #**
	REQUIRED	
PRE	Pre-existing Conditions	012
RE	Rectal Exam	041
ENR	Enrollment	070
ASR	Anoscopy and Sigmoidoscopy Results	095
SS	Specimen Storage	161
Non-DataFax	Enrollmnent Visit Eligibility	N/A
Non-DataFax	LDMS Specimen Tracking Sheet	N/A
Non-DataFax	Physical Exam	N/A
	AS NEEDED	
HTR	HIV Test Results	351
STI	STI Laboratory Results	131
Treatment 1 Visit		**VISIT CODE: 3.0**
Form Acronym	**Form Name**	**Plate #**
	REQUIRED	
RE	Rectal Exam	041
PHR	Pharmacy Randomization and First Product Dispensation*****	081
ASR	Anoscopy and Sigmoidoscopy Results	095
FU	Follow-up Visit/Phone Call	121
SS	Specimen Storage	161
Non-DataFax	Participant-Reported Follow-up Medical and Menstrual History	N/A
Non-DataFax	Physical Exam	N/A
Non-DataFax	LDMS Specimen Tracking Sheet	N/A
	AS NEEDED	
STI	STI Laboratory Results	131
HTR	HIV Test Results	351
PH	Product Hold/Discontinuation Log	410
AE	Adverse Experience Log	420
PR	Pregnancy Report and History	440
PO	Pregnancy Outcome	442-443
MV	Missed Visit	463
*****Completed by Pharmacy Staff only for those participants randomized to gel.		
Follow-Up Phone Call		**VISIT CODE: 4.0**
Form Acronym	**Form Name**	**Plate #**
	REQUIRED	
FU	Follow-up Visit/Phone Call	121

AS NEEDED		
PH	Product Hold/Discontinuation Log	410
AE	Adverse Experience Log	420
MV	Missed Visit	463
Treatment 2 Visit		**VISIT CODE: 5.0**
Form Acronym	**Form Name**	**Plate #**
REQUIRED		
SPD	Second Product Dispensation*****	082
FU	Follow-up Visit/Phone Call	121
Non-DataFax	Participant-Reported Follow-up Medical and Menstrual History	N/A
AS NEEDED		
RE	Rectal Exam	041
ASR	Anoscopy and Sigmoidoscopy Results	095
STI	STI Laboratory Results	131
SS	Specimen Storage	161
HTR	HIV Test Results	351
PH	Product Hold/Discontinuation Log	410
AE	Adverse Experience Log	420
PR	Pregnancy Report and History	440
PO	Pregnancy Outcome	442-443
MV	Missed Visit	463
Non-DataFax	Physical Exam	N/A
Non-DataFax	LDMS Specimen Tracking Sheet	N/A
*****Completed by Pharmacy Staff only for those participants randomized to gel.		
Final Clinic Visit		**VISIT CODE: 6.0**
Form Acronym	**Form Name**	**Plate #**
REQUIRED		
RE	Rectal Exam	041
SPR	Study Product Returns*****	083
ASR	Anoscopy and Sigmoidoscopy Results	095
FU	Follow-up Visit/Phone Call	121
STI	STI Laboratory Results	131
LR	Laboratory Results	151-152
SS	Specimen Storage	161
Non-DataFax	LDMS Specimen Tracking Sheet	N/A
Non-DataFax	Participant-Reported Follow-up Medical and Menstrual History	N/A
Non-DataFax	Physical Exam	N/A
AS NEEDED		
HTR	HIV Test Results	351
AE	Adverse Experience Log	420
PR	Pregnancy Report and History	440
PO	Pregnancy Outcome	442-443
MV	Missed Visit	463
*****Completed by Clinic Staff only for those participants randomized to gel.		
Follow-Up Phone Assessment Visit/Termination Visit		**VISIT CODE: 7.0**
Form Acronym	**Form Name**	**Plate #**
REQUIRED		
FU	Follow-up Visit/Phone Call	121
ESI	End of Study Inventory	489
TM	Termination	490
AS NEEDED		
AE	Adverse Experience Log	420
MV	Missed Visit	463

Interim Visit		**VISIT CODE: varies**
Form Acronym	**Form Name**	**Plate #**
REQUIRED		

IV	Interim Visit	350
AS NEEDED		
RE	Rectal Exam	041
SPR	Study Product Returns*****	083
STI	STI Laboratory Results	131
LR	Laboratory Results	151-152
HTR	HIV Test Results	351
PH	Product Hold/Discontinuation Log	410
AE	Adverse Experience Log	420
PR	Pregnancy Report and History	440
PO	Pregnancy Outcome	442-443
Non-DataFax	LDMS Specimen Tracking Sheet	N/A
Non-DataFax	Participant-Reported Follow-up Medical and Menstrual History	N/A
Non-DataFax	Physical Exam	N/A
*****Completed by Clinic Staff, as needed, only for those participants randomized to gel.		

13.3.6 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 to ensure that:

- 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 13.2.7.
- 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. This process should be described in each site's MTN-007 Data Management SOP.

13.3.7 Faxing DataFax Forms

Each site should identify which staff members will be responsible for faxing forms to SCHARP DataFax. It is important that the sites fax AE Log CRFs to SCHARP within 24 hours of site awareness of the AE, and in general, fax all other DataFax CRFs within 5 days of a completed visit. Exceptions include CRFs that capture laboratory results (these CRFs should be sent once all results have been received by the site,

acknowledging that this may take more than 5 days), log CRFs (i.e. Pre-existing Conditions and Concomitant Medications Log), and Screening Visit CRFs (these should only be faxed once the Enrollment Visit is completed and the participant has been enrolled/randomized).

It is useful to have a system to identify when each DataFax CRF has been faxed to SCHARP. If a date stamp is used to document when a 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.

Sites can also confirm the receipt of faxed CRFs at SCHARP by using the CRF Tracking System (CTS). This system generates two types of e-mail listings: 1) a listing of the number of form pages received at SCHARP and 2) a listing of the specific forms that were received at SCHARP for a given PTID and visit. Please contact the MTN-007 Project Manager if you would like to use the CRF Tracking System or for more information about the CRF Tracking System.

13.3.8 Non-DataFax Forms

MTN-007 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 13.3.1 through 13.3.4 should be applied when completing non-DataFax CRFs.

13.4 Form and Label Supply and Storage

13.4.1 Form and Specimen Label Supply

The case report forms requiring completion at each visit will be supplied to sites in form visit packets. Each packet contains all of the required CRFs for a given visit. For example, the Enrollment Visit packet contains all of the CRFs listed as “required” for the Enrollment Visit in Table 13-3. In addition to form visit packets, bulk supplies of “as needed” CRFs (for example, the AE Log form, Pregnancy Report and History form, Pregnancy Outcome form, etc.) will be provided to each site. Additional form visit packets and “loose” forms can be ordered using the MTN-007 CRF Request Form.

SCHARP will also ensure that 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. Please refer to the Laboratory section of the SSP for more information on laboratory specimen collection and labeling.

13.4.2 Form Storage

Specifications for form storage will be detailed in the site’s MTN-007 Data Management SOP. It is recommended that study staff store each participant’s CRFs in a hard-cover notebook designated as the participant’s study notebook. SCHARP will provide a template for site’s optional use in creating notebook cover and spine labels. At sites’ request, SCHARP can also provide a template that sites can use to create tab dividers for the notebooks.

It is suggested that the Concomitant Medications Log forms, Adverse Experience Log forms, and Product Hold/Discontinuation Log forms be kept in their own separate tab sections within the participant study

notebook. This makes page numbering and updating of these forms easier than if these forms were stored by visit within the participant study notebook.

13.5 Completing Interviewer-administered Forms

In order to standardize interviewer-administered data collection from site to site and to maximize data quality, it is critical that site staff 1) complete interviewer-administered forms in a consistent manner from participant to participant 2) do not influence a participant's answer, and 3) help a participant feel comfortable enough to share personal information and opinions. By doing so, site staff ensure that the data they collect is honest, accurate, and unbiased.

In MTN-007 there are two interviewer-administered forms; by this, we mean CRFs that contain questions that are required to be read aloud word-for-word to the participant as listed on the CRF. The CRFs are the non-DataFax Screening Visit Eligibility form and the Demographics form. Other forms, such as the non-DataFax Participant-Reported Baseline Medical and Menstrual History form, are completed by obtaining information from the participant, but you are not required to read the questions on these forms aloud word-for-word to the participant in order to complete the form. Completion of these forms can instead consist of more of a "discussion" with the participant rather than a structured, verbatim administration of the form questions.

Below are some guidelines and techniques that may be useful when completing both interviewer-administered forms as well as medical history forms.

Welcoming the Participant

- When a new participant arrives at the clinic, always make the participant feel comfortable. Perhaps offer him/her a glass of water or other beverage.
- Introduce yourself, and try to create a rapport (connection) between yourself and the participant to help him/her feel comfortable during the interview.
- Let the participant know what you will be talking to him/her about personal and sensitive topics as part of the visit. Some 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

All microbicide studies involve asking sensitive questions (such as questions about sexual behaviors). Your level of comfort with asking sensitive questions will affect the participant's level of comfort with answering the questions. 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 him/her know that you are listening and are aware that you are asking him/her 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 his/her behavior, he/she will be less likely to share honestly with you.

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 his/her response and proceed to the next item on a form.

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 other participants' interviews. 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.

For items with multiple sub-items, read all sub-items to the participant and record the appropriate response for each, based on participant report.

Vary your tone of voice so that you don't sound automated. Emphasize the important words in a given item, so that the participant understands the meaning of the question asked. When given the option, choose "clinical" versus "street" or "vernacular" language based on participant's preferences/cues.

Probing

Participants may not remember or know the answer to every question they are asked. 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 his/her response enough to allow for adequate documentation.

- **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, he/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, 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 the participant respond more precisely. Always repeat the participant's response in a neutral, non-judgmental way.
- **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 his/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-judgmental.
- **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/she considers accurate, it may not be specific enough for purposes of form completion. For example, an item asks for the exact number of times the participant did something and he/she answers with a range ("5 to 10"). In this case, the probe, "Can you be more specific?" is often enough to help the participant give 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 he/she may be unable to recall a specific 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 him/her feel like you don't trust his/her answers, be aware of whether he/she is giving you non-verbal cues that indicate he/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. Make sure the participant understands what you are asking and responds accordingly. 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 the interview, any items identified as missing responses 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 site clinic. For items identified as "missing", please line through the response boxes, write "missing" in the white space next to the item, and initial and date.

13.6 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 the forms are straightforward and do not require specific instructions. Therefore, specific form instructions are not always given for each item on a form. Rather, form instructions are provided only for those items requiring additional clarification for purposes of form completion.

Below are some additional instructions for the **Pre-existing Conditions, Concomitant Medications Log, Laboratory** Results, and **Adverse Experience Log** case report forms.

Pre-existing Conditions and Concomitant Medications Log forms:

- Each time a new entry is added or an existing entry is modified, fax the form page to SCHARP DataFax. Do **not** wait to complete all entries on a page before faxing it to SCHARP DataFax.

Laboratory Results (LR) form:

- Depending on a site's normal reference ranges, it is possible that a participant can have a value that falls within the normal range, but is still gradable per the DAIDS Toxicity Table. Always refer to the DAIDS Toxicity Table when determining whether or not a lab value is gradable and should be reported as an AE.
- If a lab value is gradable per the DAIDS Toxicity Table, regardless of whether the specimen was collected at screening, enrollment, or during follow-up, record the severity grade in the "**Severity Grade**" box. Record the "**AE Log Page #**" if the gradable lab value is reportable as an AE or mark the "**Not Reportable as an AE**" box. If a severity grade is recorded in the "Severity Grade" box, either an "AE Log Page #" must be recorded or the "Not reportable as an AE" box must be marked. The same "AE Log Page #" may be recorded for the same item on SL forms completed at different visits, for example, if a lab value AE persists at the same severity across study visits.

Adverse Experience Log (AE Log):

- Fax AE Log pages to SCHARP as soon as they are first completed. Ideally, SCHARP would like to receive AE Log forms within 1 day of the AE's "Date Reported to Site". Do **not** wait until a given 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 has an outcome (the AE resolves, the AE is grade 5 - death, or the AE increases in severity/frequency), update items 6 and 6a of the **original** AE Log form page. Initial and date all additions, and any other changes made to the form page, and refax the page to SCHARP.
- For AEs of gradable lab results (e.g., "Increased ALT"), the date the lab result/report is received at the site clinic is recorded as the "Date Reported to Site" on the AE Log. The date of specimen collection is recorded for **item 2** ("Onset Date"). For these AEs, **item 6a** "Status/Outcome Date" is the collection date of the follow-up specimen that yields a non-gradable result, or a result of increased severity (thus requiring completion of a new AE Log).
- 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.
- For **item 4**, note that if "not related" is marked, you must record the reason the AE is determined to be "not related" in the Comments section 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". Note that for participants assigned to "no treatment (no gel)", item 4 of the AE Log form should always be "not related" (and in the "Comments" section, there should be a note similar to "#4 = ppt in no gel arm").
- For **item 7**, note that if the AE results in a new or prolonged hospitalization, the AE meets the criteria for a "serious" AE and EAE reporting. In this case, items 8 and 9 of the AE Log form should be marked "yes".
- For **item 10,** note that the Visit Code recorded in item 10 is the visit code associated with the date in the "Date Reported to Site" field. AE Log forms that report lab values as AEs are the one exception - for these forms, record the Visit Code associated with the "Onset Date" (since the "Date Reported to Site" may be after the "Onset Date" for lab AEs, and may not be associated with a Visit Code).
- 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).
- There may be situations where an AE reported on an Adverse Experience Log form needs to be deleted (for example, in the case where a condition is thought to be an AE and is later determined to have been pre-existing). To mark an AE for deletion, draw a diagonal line across the entire AE Log 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 completed for the participant, if any. Do not renumber AE Log pages after faxing unless specifically instructed to do so by SCHARP.

13.7 Case Report Forms

This section contains each MTN-007 case report form developed for the study. The forms are presented in alphabetical order by form title.

SAMPLE: DO NOT FAX TO DATAFAX

Note: Number pages sequentially (001, 002, 003) for each participant. **Page** ☐☐☐

MTN007 (172) AE-1 (460)

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.

2. Onset Date

☐☐ ☐☐☐ ☐☐
dd *MMM* *yy*

3. Severity

- ☐ Grade 1 – Mild
- ☐ Grade 2 – Moderate
- ☐ Grade 3 – Severe
- ☐ Grade 4 – Potentially life-threatening
- ☐ Grade 5 – Death

4. Relationship to Study Product

- ☐ Related
- ☐ Not related

Record rationale or alternative etiology in Comments.

5. Study Product Administration

- ☐ No change
- ☐ Held
- ☐ Permanently discontinued
- ☐ N/A

6. Status/Outcome

- ☐ Continuing
- ☐ Resolved
- ☐ Death
- ☐ Severity/frequency increased *Report as a 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.*

		yes	*no*
8.	Is this an SAE according to ICH guidelines?	☐	☐
9.	Has/will this AE be reported as an EAE?	☐	☐
10.	At which visit was this AE first reported? ..... *Visit code required (regular or interim).*	☐☐.☐	
11.	Was this AE a worsening of a pre-existing condition?	☐	☐

Comments: _____

_____

_____

☐ ☐ ☐ ☒ 18-AUG-10

N:\hivnet\forms\MTN_007\forms\m007_std_AE_14may10.fm

0 1
Language

Staff Initials / Date

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 Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies)*. AEs not included in these tables will be graded by the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences*.
- **Item 4:** Mark the assessment of the relationship between the AE and the study agent. Mark "Related" if there is a reasonable possibility that the AE may be related to the study agent. Mark "Not related" if there is not a reasonable possibility that the AE is related to the study agent. If "Not related," record an alternative etiology, diagnosis, or explanation in the "Comments" field. For more information, refer to the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2*.
- **Item 5:**
  - ***No change***: Mark if the participant is expected to continue to use study product and the AE does NOT result in a study product hold or permanent discontinuation.
  - ***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 participant is in the "no gel" group. Also mark if the AE occurred after the participant had completed all administrations 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. Update EAE form if applicable. 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 protocol and the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2*.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐.☐ 1

MTN007 (172) ASR-1 (095)

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Anoscopy and Sigmoidoscopy Results

Visit Date

☐☐ ☐☐☐ ☐☐

dd *MMM* *yy*

ANOSCOPY

yes *no, specify:* _____

1. Was an anoscopy performed at this visit? ..... ☐ ☐ → ***If no, go to item 4.***

normal findings *abnormal findings*

2. Anal canal findings: ..... ☐ ☐

→ ***If normal findings, go to item 3.***

2a. Abnormal anal canal findings: *Mark all that apply.*

☐ Warts ☐ Ulceration ☐ Hemorrhoids

☐ Fissure ☐ Bleeding ☐ Other abnormal findings, specify: _____

At Enrollment, update Pre-existing Conditions form when applicable.
During follow-up, complete or update AE Log when applicable.

normal findings *abnormal findings*

3. Rectal mucosa findings: ..... ☐ ☐

→ ***If normal findings, go to item 4.***

3a. Abnormal rectal mucosa findings: *Mark all that apply.*

☐ Erythema ☐ Friability ☐ Hemorrhoids

☐ Abnormal vessels ☐ Bleeding ☐ Other abnormal findings, specify: _____

☐ Ulceration ☐ Discharge

At Enrollment, update Pre-existing Conditions form when applicable.
During follow-up, complete or update AE Log when applicable.

SIGMOIDOSCOPY

yes *no, specify:* _____

4. Was a sigmoidoscopy performed at this visit? ☐ ☐ → ***If no, end of form.***

normal findings *abnormal findings*

5. Sigmoidoscopy findings: ..... ☐ ☐

→ ***If normal findings, end of form.***

5a. Abnormal sigmoidoscopy findings: *Mark all that apply.*

☐ Erythema ☐ Bleeding ☐ Other abnormal findings, specify: _____

☐ Abnormal vessels ☐ Discharge

☐ Ulceration ☐ Polyp

☐ Friability ☐ Hemorrhoids

At Enrollment, update Pre-existing Conditions form when applicable.
During follow-up, complete or update AE Log when applicable.

Anoscopy and Sigmoidoscopy Results (ASR-1)

Purpose: This form is used to document the findings from the Anoscopy and the Sigmoidoscopy procedures. Anoscopy procedures are required at Enrollment, Treatment 1, and the Final Clinic Visit. Sigmoidoscopy procedures are required at Enrollment, Treatment 1, and the Final Clinic Visit.

General Information/Instructions:

- **Visit Code:** Record the visit code assigned to this visit. Refer to the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.

Item-specific Instructions:

- **Items 2a, 3a, and 5a:** Mark the box to the left of each abnormal finding observed. If an observed abnormal finding is not listed, mark the “Other abnormal findings, specify” box and describe the abnormal finding on the line provided.

SAMPLE: DO NOT FAX TO DATAFAX

Note: Number pages sequentially (01, 02, 03) for each participant **Page** ☐☐

MTN007 (172) 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.***

1. **Medication** *(generic name)* | **Staff Initials/Log Entry Date**

Indication

Taken for a reported AE? ☐ *yes* ☐ *no* → ***Record AE Log page(s):*** ☐☐☐ ☐☐☐ ☐☐☐ ☐☐☐

Date Started ☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*) **Date Stopped** ☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*) **OR** ☐ Continuing at end of study

Frequency *Mark only one.* ☐ *prn* ☐ *qd* ☐ *tid* ☐ *qhs* ☐ *qxh: every* ☐☐ *hrs* ☐ *once* ☐ *bid* ☐ *qid* ☐ *other, specify:* _____

Dose/Units

Route *Mark only one.* ☐ *PO* ☐ *IM* ☐ *IV* ☐ *TOP* ☐ *IHL* ☐ *VAG* ☐ *REC* ☐ *other, specify:* _____

2. **Medication** *(generic name)* | **Staff Initials/Log Entry Date**

Indication

Taken for a reported AE? ☐ *yes* ☐ *no* → ***Record AE Log page(s):*** ☐☐☐ ☐☐☐ ☐☐☐ ☐☐☐

Date Started ☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*) **Date Stopped** ☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*) **OR** ☐ Continuing at end of study

Frequency *Mark only one.* ☐ *prn* ☐ *qd* ☐ *tid* ☐ *qhs* ☐ *qxh: every* ☐☐ *hrs* ☐ *once* ☐ *bid* ☐ *qid* ☐ *other, specify:* _____

Dose/Units

Route *Mark only one.* ☐ *PO* ☐ *IM* ☐ *IV* ☐ *TOP* ☐ *IHL* ☐ *VAG* ☐ *REC* ☐ *other, specify:* _____

3. **Medication** *(generic name)* | **Staff Initials/Log Entry Date**

Indication

Taken for a reported AE? ☐ *yes* ☐ *no* → ***Record AE Log page(s):*** ☐☐☐ ☐☐☐ ☐☐☐ ☐☐☐

Date Started ☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*) **Date Stopped** ☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*) **OR** ☐ Continuing at end of study

Frequency *Mark only one.* ☐ *prn* ☐ *qd* ☐ *tid* ☐ *qhs* ☐ *qxh: every* ☐☐ *hrs* ☐ *once* ☐ *bid* ☐ *qid* ☐ *other, specify:* _____

Dose/Units

Route *Mark only one.* ☐ *PO* ☐ *IM* ☐ *IV* ☐ *TOP* ☐ *IHL* ☐ *VAG* ☐ *REC* ☐ *other, specify:* _____

Concomitant Medications Log (CM-1)

Purpose: All medication(s) that are used by the participant during the study including the protocol-defined screening period), 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.

General Information/Instructions: When to fax this form:

- once the participant has enrolled in the study;
- 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.

Item-specific instructions:

- **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 from Screening through the Enrollment visit. This box should only be marked on Page 01.
- **No medications taken throughout study:** Mark this box at the Termination visit if no medications were taken by the participant throughout the entire study.
- **Medication:** For combination medications, record 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 are required.
- **Frequency:** Below is a list of common 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

- **Route:** Below is a list of common route abbreviations:

PO oral	**IM** intramuscular	**IV** intravenous	**TOP** topical	**IHL** inhaled	**VAG** vaginal	**REC** rectal

- **Dose/Units:** If the participant does not know the dose or units, draw a single line through the blank response box 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).

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) 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?..... dd MMM yy → If unknown, record age: years

2. What is your gender? ..... male ☐ female ☐

3. Do you consider yourself to be Latino/a or of Hispanic origin? ..... yes ☐ no ☐

4. What is your race? *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. other, specify: _____

Demographics (DEM-1)

Purpose: This interviewer-administered form is used to collect participants' demographic information.

General Information/Instructions: This form is faxed to SCHARP DataFax only if the participant enrolls in the study, and only after completion of his/her Enrollment Visit.

- **Visit Code:** There is no visit code field on this form since this form is only administered once at screening.
- ***Note:*** *If a participant is being re-screened, a new Demographics form must be completed as part of the subsequent screening attempt. See the Study-Specific Procedures (SSP) Manual for more instructions regarding re-screening, form completion, and transmission procedures.*

Item-specific Instructions:

- **Item 1:** If any portion of the date of birth is unknown, record age at time of screening. If age is unknown, record the participant's best estimate of his/her age. Do not complete both answers.
- **Item 2:** This item must be self-identified by the participant.
- **Item 3:** This item is based on self-definition. Per NIH policy, Latino/a or Hispanic includes a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.
- **Item 4:** Record the participant's race based on self-definition. In the case of mixed race, mark all that apply and/or "other" and indicate the mixed race background. Per NIH policy, Latino/a is considered an ethnic group and not a race and should not be entered in item 4f.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) ESI-1 (489)

Participant ID

Site Number – Participant Number – Chk

End of Study Inventory

Form Completion Date

dd MMM yy

1. What is the **highest** visit code (scheduled or interim) for this participant, recorded on a form submitted via DataFax?..... *visit code* ☐☐.

2. How many interim visits were conducted for this participant during the study and recorded on a form submitted via DataFax?..... *# of interim visits* ☐☐☐

3. Indicate the **highest** page number submitted for this participant for each of the following forms:

3a.	Adverse Experience Log	*page #* ☐☐☐	**OR**	*no pages submitted* ☐
3b.	Concomitant Medications Log	*page #* ☐☐		
3c.	Pre-existing Conditions	*page #* ☐☐		
3d.	Product Hold/Discontinuation Log	*page #* ☐☐	**OR**	*no pages submitted* ☐

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

01 Language

Staff Initials / Date

End of Study Inventory (ESI-1)

Purpose: This form is used to confirm that SCHARP has received all study data for a given participant.

General Information/Instructions: Complete this form once for each enrolled participant after the participant has terminated from the study (as documented by a Termination form).

Item-specific instructions:

- **Form Completion Date:** A complete date is 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 3d:** Record the highest page number of the Product Hold/Discontinuation Log submitted for this participant, even if that page was marked for deletion.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) ENR-1 (070)

Participant ID

☐☐☐ – ☐☐☐☐☐ – ☐

Site Number Participant Number Chk

Enrollment

1. Was the participant, based on all inclusion and exclusion criteria, eligible for the study? ..... yes ☐ no ☐ → ***If no, end of form.***

2. Date the informed consent form for enrollment was marked or signed: ..... ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

3. Was the participant able and willing to provide written informed consent for specimen storage and future research?..... yes ☐ no ☐ → ***If no, go to item 4.***

   3a. Date the informed consent form for specimen storage and future research was marked or signed: ..... ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

4. Is this a replacement participant? ..... yes ☐ no ☐ → ***If no, go to item 5.***

   4a. PTID of participant being replaced: ..... ☐☐☐ – ☐☐☐☐☐ – ☐ (Site Number – Participant Number – Chk)

5. Clinic randomization envelope number: ..... ☐☐☐

   5a. Date assigned: ..... ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

   5b. Time assigned: ..... ☐☐ : ☐☐ *24-hour clock* (hr min)

6. To which study group was the participant assigned?..... gel ☐ no gel ☐

7. Did the participant complete the CASI Baseline Behavioral Questionnaire (BBQ) at this visit? ..... yes ☐ no ☐ → ***If no, specify in Comments. End of form.***

   7a. Date CASI BBQ was completed: ..... ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

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0 1 Language

Staff Initials / Date

Enrollment (ENR-1)

Purpose: 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.

General Information/Instructions: This form is faxed to SCHARP DataFax only if the participant is enrolled (that is, he/she is assigned a clinic randomization envelope), and only after completion of the Enrollment Visit.

- **Visit Code:** There is no visit code field on this form since this form is only completed once at the Enrollment Visit.

Item-specific Instructions:

- **Item 1:** If response to this item is "no" (the participant was not eligible for this study), end the form. Do NOT fax this or any other forms completed for this participant to SCHARP DataFax.
- **Item 2:** Record a complete date.
- **Item 3:** Mark "yes" only if the participant gave consent to have his/her lab specimens stored for future research testing.
- **Item 3a:** Record a complete date.
- **Item 5:** Record the 3-digit envelope number present on the clinic randomization envelope assigned to this participant. If this is a replacement participant, record the clinic randomization envelope number of the participant being replaced.
- **Item 5a:** Record the date the clinic randomization envelope was assigned to the participant. This date should match the "date assigned" recorded for this envelope on the MTN 007 Clinic Randomization Envelope Tracking Record. If this is a replacement participant, record the date the replacement prescription was completed.
- **Item 5b:** Record the time the clinic randomization envelope was assigned to the participant. Use a 24-hour clock to record time. For example, if the clinic randomization envelope was opened at 2:24 p.m., record 14:24. This time should match the "time assigned" recorded for this envelope on the MTN 007 Clinic Randomization Envelope Tracking Record. If this is a replacement participant, record the time the replacement prescription was completed.
- **Item 6:** Record the participant's randomization assignment present on the prescription. If this is a replacement participant, record the assignment given to the participant being replaced.
- **Item 7:** Completion of the CASI Baseline Behavioral Questionnaire (BBQ) is required for all participants at the Enrollment Visit. If the required questionnaire was not done, specify the reason on the Comments lines.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) FU-1 (121)

Visit Code . 1

Participant ID

Site Number – Participant Number – Chk

Follow-up Visit/Phone Call

Visit Date

dd MMM yy

1. Were any **new** adverse experiences reported at this visit/phone call? ..... yes ☐ no ☐ → ***If no, go to item 2.***

   1a. How many **new** AE Log pages were completed for this visit/phone call? ..... ☐☐ *# of **new AE Log** pages*

2. Was a **new** study product hold/discontinuation initiated at this visit/phone call? ..... yes ☐ no ☐ → ***If no, go to item 3.***

   2a. How many **new** Product Hold/Discontinuation Log pages were completed for this visit/phone call? ..... ☐☐ *# of **new Product Hold/ Discontinuation Log** pages*

3. Did the participant complete the CASI Product Acceptability Questionnaire at this visit? ..... yes ☐ no ☐ not required ☐ → ***If no, specify in Comments. If no or not required, go to item 4.***

   3a. Date CASI Product Acceptability Questionnaire was completed: ..... ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

4. Was an hCG pregnancy test done at this visit? ..... yes ☐ no ☐ not required ☐ → ***If no, specify in Comments. If no or not required, end of form.***

   4a. Date test done: ..... ☐☐ ☐☐☐ ☐☐ (dd MMM yy)

   4b. hCG pregnancy test result: ..... negative ☐ positive ☐ → ***If newly positive, complete Pregnancy and History Report and Product Hold/ Discontinuation Log.***

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

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0 1 Language

Staff Initials / Date

Follow-up Visit/Phone Call (FU-1)

Purpose: This form is used to document the required (regularly scheduled) follow-up visits/phone calls. It is completed at each regularly scheduled follow-up visit/phone call, regardless of whether the visit/phone call is conducted within the protocol-specified window or made up outside the visit window.

General Information/Instructions:

- **Visit Code:** Record the visit code assigned to the visit. Refer to the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.

Item-specific Instructions:

- **Item 1:** Mark the "yes" box if a new (previously unreported) AE is observed or reported at this visit/phone call. If the box is marked "yes," record in item 1a how many **new** Adverse Experience Log pages were completed for this visit/phone call. 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 2:** Mark the "yes" box if a product hold/discontinuation is initiated at this visit/phone call. If the box is marked "yes," record in item 2a how many **new** Product Hold/Discontinuation Log pages were completed for this visit/phone call. For example, if two new product holds were reported, record "02." Note that the Visit Code recorded in item 1 of these two PH Log pages should be the same as the Visit Code recorded on this form.
- **Item 3:** Completion of the CASI Product Acceptability Questionnaire is required only at the Final Clinic Visit for participants in the "gel" group. If the questionnaire is required but not done, mark the "no" box and specify the reason on the Comments lines. If the questionnaire is not required, mark the "not required" box. If the participant is in the "no gel" group, also mark the "not required" box.
- **Item 4:** Pregnancy testing is required at all clinic visits for females of childbearing potential. If a pregnancy test result is not available (i.e., the specimen was not collected and/or the test was not done), mark the "no" box and record the reason why on the Comments lines. If the participant is male or is a female who is not of childbearing potential, mark the "not required" box.
- **Item 4b:** A Pregnancy Report and History form must be completed for each new pregnancy. Once a participant tests positive for hCG urine pregnancy and a Pregnancy Report and History form (PR-1) is completed for this pregnancy, subsequent positive pregnancy test results should not be recorded on a new PR-1 unless they represent a new pregnancy.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) HTR-1 (351)

Visit Code ☐.☐ 1

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 or indeterminate, contact MTN Network Lab.

Sample 2

2. HIV Western Blot or IFA

Not done/ Not collected ☐ **Specimen Collection Date** ☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*)

negative ☐ *positive* ☐ *indeterminate* ☐

If negative or indeterminate, contact MTN Network Lab.

FINAL HIV STATUS

3. Final HIV status: ..... *negative* ☐ *positive* ☐ *other, specify:* _____

If positive at Screening, participant is ineligible. If positive during follow-up, complete Product Hold/Discontinuation Log.

Comments: _____

☐☐☐☒ 04-SEP-09

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01 Language

_____ Staff Initials / Date

HIV Test Results (HTR-1)

Purpose: 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 during study follow-up.

General Information/Instructions: 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 3 has been completed.

- **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. Record the reason why the result is not available on the Comments lines at the bottom of the form.

Item-specific Instructions:

- **Item 3:** 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 provide a 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:** Document any problems or reasons why expected results are not available (for example, if the sample was lost or damaged), on the lines provided.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) 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, if applicable.***
- ☐ 1b. phone call from participant to report new symptoms → ***Complete Adverse Experience Log, if applicable.***
- ☐ 1c. follow-up of symptoms and/or AE(s) → ***Update Adverse Experience Log, if applicable.***
- ☐ 1d. participant needs study product
- ☐ 1e. participant is returning unused study product
- ☐ 1f. other, specify: _____

2. Besides this Interim Visit form, what other DataFax forms were completed at this visit? *Mark "none" or all that apply.*

- ☐ 2a. none
- ☐ 2b. Rectal Exam
- ☐ 2c. Laboratory Results
- ☐ 2d. STI Laboratory Results
- ☐ 2e. Adverse Experience Log (new) → 2e1. How many **new** AE Log pages were completed for this visit? *# of pages* ☐☐
- ☐ 2f. Product Hold/Discontinuation Log (new) → 2f1. How many **new** PH Log pages were completed for this visit? ☐☐
- ☐ 2g. other, specify: _____

3. Was an hCG pregnancy test done at this visit? ..... *yes* ☐ *no* ☐ *not required* ☐ → ***If no, specify in Comments. If no or not required, end of form.***

3a. hCG pregnancy test result: ..... *negative* ☐ *positive* ☐ → ***If newly positive, complete Pregnancy Report and History and Product Hold/ Discontinuation Log.***

Comments: _____

_____

_____

☐☐☐☒ 04-SEP-09

01 Language

Staff Initials / Date

Interim Visit (IV-1)

Purpose: Complete this form when an Interim Visit occurs during study follow-up.

General Information/Instructions: Any other forms completed for this visit must have the same Visit Code as this Interim Visit form.

- **Visit Code:** The following guidelines should be used for assigning the interim visit code:
  - Record the visit code for the most recent scheduled regular visit. For example, if the most recent scheduled regular visit was Treatment 1 (Visit Code = 3.0), record "3" to the left of the decimal point in the visit code field.
  - Record the number that corresponds to the Interim Visit in the second box (the box to the right of the decimal point):

    X.1 = First Interim Visit after the most recent scheduled regular visit.

    X.2 = Second Interim Visit after the most recent scheduled regular visit.

Item-specific instructions:

- **Item 1d:** If participant received additional study product, record the amount of study product dispensed on the Comments line.
- **Item 1e:** If participant returned unused study product, record the amount of unused study product that was returned on the Comments line.
- **Item 2:** Note that marking a box other than "none" indicates that a DataFax form with the same visit code as this form will be faxed to SCHARP DataFax.
  - **Item 2a:** Mark the "none" box if the Interim Visit form is the **only** DataFax form completed for this visit.
  - **Item 2e:** 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 how many **new** AE Log pages were completed for this visit in item 2e1. 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 2f:** Mark this box if a new (previously unreported) product hold/discontinuation is reported at this visit. If the box to the left of "Product Hold/Discontinuation Log (new)" is marked, record how many **new** PH Log pages were completed for this visit in item 2f1. For example, if two new product holds were reported, record "02." Note that the Visit Code recorded in item 1 of these two PH Log pages should be the same as the Visit Code recorded on this form.
- **Item 3:** Pregnancy testing is done at interim visits only if clinically indicated (and only for females of childbearing potential). If a pregnancy test result is not available (i.e., the specimen was not collected and/or the testing was clinically indicated but not done), mark the "no" box and record the reason why on the Comments lines. If the participant is male or is a female who is not of childbearing potential, mark the "not required" box.
  - **Item 3a:** A Pregnancy Report and History form must be completed for each new 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.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) LR-1 (151)

Visit Code ☐.☐ 1

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

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
☐	1a. WBC	☐☐☐.☐ *x10³/mm³*	☐	☐☐☐	OR ☐
☐	1b. Hemoglobin	☐☐.☐ *g/dL*	☐	☐☐☐	OR ☐
☐	1c. Hematocrit	☐☐.☐ *%*			
☐	1d. MCV	☐☐☐.☐ *fL*			
☐	1e. Platelets	☐☐☐☐.☐ *x10³/mm³*	☐	☐☐☐	OR ☐

Not done/ Not collected ☐ **Alternate Collection Date** *dd* ☐☐ *MMM* ☐☐☐ *yy* ☐☐

2. DIFFERENTIAL

Not reported		*percentage*		Absolute Count *cells/mm³*	Severity Grade *If applicable*	AE Log Page #	Not reportable as an AE
☐	2a. Neutrophils	☐☐.☐	AND	☐☐☐☐☐	☐	☐☐☐	OR ☐
☐	2b. Lymphocytes			☐☐☐☐	☐	☐☐☐	OR ☐
☐	2c. Monocytes			☐☐☐☐			
☐	2d. Eosinophils			☐☐☐☐			
☐	2e. Basophils			☐☐☐☐			

Not done/ Not collected ☐ **Alternate Collection Date** *dd* ☐☐ *MMM* ☐☐☐ *yy* ☐☐

3. LIVER FUNCTION TESTS

		U/L	Severity Grade *If applicable*	AE Log Page #	Not reportable as an AE
☐	3a. AST (SGOT)	☐☐☐☐	☐	☐☐☐	OR ☐
☐	3b. ALT (SGPT)	☐☐☐☐	☐	☐☐☐	OR ☐

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

0 1 Language

Staff Initials / Date

Laboratory Results (LR-1)

Purpose: This form is used to document local safety laboratory results of specimens collected during screening and study follow-up.

General Information/Instructions: 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 (if ongoing at Enrollment), or an adverse experience on an Adverse Experience (AE) Log (for follow-up visit test result(s) only).

- **Visit Code:** Record the visit code assigned to the visit. Refer to the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **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. Record a complete date.
- **Alternate Collection Date**: This date is to be completed ONLY if the specimen is collected after the Initial Specimen Collection Date for this same visit. Record a complete date.
- **Not Done/Not Collected:** For every test, mark *either* the "Not done/Not collected" box *or* enter a test result. If the "Not Done/ Not Collected" box is marked, record reason on the Comments line.
- **Not reported:** If a test was done but a given result was not reported, mark the "Not reported" box.

Results Reporting:

- 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) Manual for conversion instructions.
- If the site lab does not report results to the same level of precision allowed on the CRF, record a zero (0) in the box(es) to the right of the decimal point. For example, a lab-reported hematocrit value of 30% would be recorded as 30.0%.
- 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.

Severity Grade:

- If any abnormal laboratory values meet the criteria for severity grade 1 or greater, according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Addenda 1 and 3)*, 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 (Addenda 1 and 3)*. Per the protocol-specific AE reporting requirements, report this as an AE, as appropriate, and grade it according to the *DAIDS Table (Addenda 1 and 3)*.

AE Log Page #: If the lab value is reportable as an AE, record the page number of the AE Log that is most closely associated with the abnormal lab value.

Not Reportable as an AE: Only mark this box if the lab value is gradable per the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Addenda 1 and 3)*, 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-specific Instructions:

- **Item 2a:** Neutrophils must be recorded as both a percentage and an absolute count.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code . 1

MTN007 (172) LR-2 (152)

Participant ID

Site Number – Participant Number – Chk

Laboratory Results

4. RENAL FUNCTION TESTS

Not done/ Not collected	Alternate Collection Date dd MMM yy			mg/dL	Severity Grade If applicable	AE Log Page #	Not reportable as an AE
☐				4a. Creatinine .			OR ☐
☐				4b. BUN		mg/dL	

5. DIPSTICK URINALYSIS TESTS

Not done	Alternate Collection Date dd MMM yy			negative	positive
☐				5a. Leukocyte esterase (LE) ..... ☐	☐
☐				5b. Nitrites ..... ☐	☐

Not done		negative	trace	1+	2+	3+	4+	Severity Grade If applicable	AE Log Page #	Not reportable as an AE
☐	5c. Protein	☐	☐	☐	☐	☐	☐	☐		OR ☐
☐	5d. Glucose	☐	☐	☐	☐	☐	☐	☐		OR ☐

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

0 1 Language

Staff Initials / Date

Laboratory Results (LR-2)

Item-specific Instructions:

- **Item 5:** If a dipstick urinalysis was done but a given result was not reported, mark the "Not done/Not collected" box.
- **Items 5a and 5b:** If the result is negative or trace, mark the "negative" box. If the result is 1+ or greater, mark the "positive" box.
- **Item 5d:** Grade the severity of the urine glucose value according to the "Proteinuria, random collection" row of the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code . 0 1

MTN007 (172) MV-1 (463)

Participant ID

Site Number – Participant Number – Chk

Missed Visit

Form Completion Date

dd MMM yy

1. Target Visit Date: dd MMM yy

2. Reason visit was missed. *Mark only one.*

- ☐ 2a. unable to contact participant
- ☐ 2b. unable to schedule appointment(s) within allowable window
- ☐ 2c. participant refused visit
- ☐ 2d. participant incarcerated
- ☐ 2e. participant admitted to a health care facility → ***Complete Adverse Experience Log, if applicable.***
- ☐ 2f. participant withdrew from the study → ***Complete Termination form.***
- ☐ 2g. participant deceased → ***Complete Termination form. Complete Adverse Experience Log and EAE Reporting form.***
- ☐ 2h. other, specify: _____
- ☐ 2i. participant relocated

Comments: _____

Missed Visit (MV-1)

Purpose: Complete this form whenever an enrolled participant misses a required visit according to the visit windows outlined in the protocol and Study-Specific Procedures (SSP) Manual.

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.

Item-specific Instructions:

- **Visit Code:** Record the Visit Code of the visit that was missed.
- **Form Completion Date:** 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 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 007 (172) PRC-1 (466)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number Participant Number Chk

Participant Receipt

Form Completion Date

[ ][ ] [ ][ ][ ] [ ][ ]

dd *MMM* *yy*

***Note: Do not** assign a new Participant ID. Record the Participant ID assigned by the original study site.*

1. Name of receiving study site: _____

2. Name of transferring study site: _____

3. Date informed consent signed at receiving study site: [ ][ ] [ ][ ][ ] [ ][ ]

dd *MMM* *yy*

yes *no*

4. Did participant provide informed consent for specimen storage at receiving study site? ☐ ☐ → ***If no, end of form.***

4a. Date informed consent for specimen storage signed: [ ][ ] [ ][ ][ ] [ ][ ]

dd *MMM* *yy*

Comments: _____

_____

☐ ☐ ☐ ☒ 04-SEP-09

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[0][1] Language

_____ Staff Initials / Date

Participant Receipt (PRC-1)

Purpose: Complete this form when a transferred participant has provided informed consent at the receiving study clinic/site.

General Information/Instructions: The Participant Receipt form is completed by the receiving site (the site at which the participant will be continuing his or her study visits).

For more information on Participant Transfer and Receipt, refer to the protocol, and/or the Study-Specific Procedures (SSP) Manual.

Item-specific instructions:

- **Participant ID: Do not** assign a new Participant ID. Record the Participant ID assigned by the original study site.
- **Item 3:** A complete date is required.
- **Item 4a:** A complete date is required.

SAMPLE: DO NOT FAX TO DATAFAX

MTN 007 (172) PT-1 (465)

Participant ID

☐☐☐ – ☐☐☐☐☐ – ☐

Site Number Participant Number Chk

Participant Transfer

Form Completion Date

☐☐ ☐☐☐ ☐☐

dd *MMM* *yy*

1. Name of transferring study site: _____

2. Name of receiving study site: _____

3. Visit Code of last completed contact with participant: ☐.☐

4. Date participant records were sent to receiving study site: ☐☐ ☐☐☐ ☐☐

dd *MMM* *yy*

Comments: _____

_____

☐ ☐ ☐ ☒ 04-SEP-09

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Language

_____
Staff Initials / Date

Participant Transfer (PT-1)

Purpose: Complete this form when a participant is transferring to another study clinic/site.

General Information/Instructions: The Participant Transfer form is completed by the transferring site (the site that the participant is leaving).

For more information on Participant Transfer and Receipt, refer to the protocol, and/or the Study-Specific Procedures (SSP) Manual.

Item-specific instructions:

- **Item 4:** A complete date is required.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) PRE-1 (012)

Note: *Number pages sequentially (01, 02, 03) for each participant.*

Page ☐☐

Participant ID

☐☐☐ – ☐☐☐☐☐ – ☐

Site Number Participant Number Chk

Pre-existing Conditions

☐ **No pre-existing conditions reported or observed.** _____ Staff Initials / Date → ***End of form. Fax to SCHARP DataFax.***

1.

Description	*MMM* *yy* **Date of Diagnosis/ Surgery** ☐☐☐ ☐☐
Comments	*yes* *no* **Is condition ongoing?** ☐ ☐ _____ Staff Initials / Date

2.

Description	*MMM* *yy* **Date of Diagnosis/ Surgery** ☐☐☐ ☐☐
Comments	*yes* *no* **Is condition ongoing?** ☐ ☐ _____ Staff Initials / Date

3.

Description	*MMM* *yy* **Date of Diagnosis/ Surgery** ☐☐☐ ☐☐
Comments	*yes* *no* **Is condition ongoing?** ☐ ☐ _____ Staff Initials / Date

4.

Description	*MMM* *yy* **Date of Diagnosis/ Surgery** ☐☐☐ ☐☐
Comments	*yes* *no* **Is condition ongoing?** ☐ ☐ _____ Staff Initials / Date

5.

Description	*MMM* *yy* **Date of Diagnosis/ Surgery** ☐☐☐ ☐☐
Comments	*yes* *no* **Is condition ongoing?** ☐ ☐ _____ Staff Initials / Date

6.

Description	*MMM* *yy* **Date of Diagnosis/ Surgery** ☐☐☐ ☐☐
Comments	*yes* *no* **Is condition ongoing?** ☐ ☐ _____ Staff Initials / Date

Pre-existing Conditions (PRE-1)

Purpose: This form is used to document the participant's pre-existing medical conditions.

General Information/Instructions: Only medical conditions experienced up to study product initiation should be recorded unless otherwise specified in the protocol or Study-Specific Procedure (SSP) Manual. Include current medical conditions and any ongoing conditions such as mental illness, alcoholism, drug abuse, and chronic conditions (controlled or not controlled by medication).

- **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).

Item-specific Instructions:

- **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.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) PO-1 (442)

Visit Code ☐.☐ Outcome Number ☐

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Pregnancy Outcome

☐ **Outcome unobtainable**
→ ***End of form.***

If Outcome Number recorded above is 2 or greater, go to item 2.

1. How many pregnancy outcomes resulted from this reported pregnancy?..... ☐

2. Outcome Date: ..... *dd* ☐☐ *MMM* ☐☐☐ *yy* ☐☐

3. Place of delivery/outcome:
   - ☐ home
   - ☐ hospital
   - ☐ clinic
   - ☐ unknown
   - ☐ other, specify: _____

4. Specify Outcome: *Mark only one.*
   - ☐ 4a. full term live birth (≥ 37 weeks)
   - ☐ 4b. premature live birth (< 37 weeks)

   → 4a1. **Method:** *C-section* ☐ *vaginal* ☐
   - ☐ 4c. stillbirth/intrauterine fetal demise (≥ 20 weeks)
   - ☐ 4d. spontaneous abortion (< 20 weeks)
   - ☐ 4e. ectopic pregnancy
   - ☐ 4f. therapeutic/elective abortion
   - ☐ 4g. other, specify: _____

5. Provide a brief narrative of the circumstances: _____

_____

_____

Pregnancy Outcome (PO-1)

Purpose: This form is used to report pregnancy outcome information for a pregnancy reported post-enrollment. Complete this form when information about a pregnancy outcome becomes available to study staff or when it is determined that pregnancy outcome is unobtainable.

General Information/Instructions: A Pregnancy Outcome form is required for each Pregnancy Report and History form that is completed for a participant.

Item-specific Instructions:

- **Visit Code:** Record the visit code of the participant's corresponding Pregnancy Report and History form.
- **Outcome Number:** A pregnancy outcome can be an infant or fetus. The conception of twins, for example, will result in reporting of two outcomes. For pregnancies resulting in one pregnancy outcome, record "1" here. For pregnancies with multiple outcomes, record the outcome number matching the outcome data recorded on the form.
- **Outcome unobtainable:** If it is determined that an outcome is unobtainable (i.e., the participant refuses further contact), mark the "Outcome unobtainable" box at the top of the page and fax both pages of this form to SCHARP DataFax.
- **Item 1:** If a pregnancy results in two outcomes, complete two Pregnancy Outcome forms (one for each outcome). Both Outcome forms will have the same visit code but different outcome numbers (for example, one Outcome form will have an outcome number =1 and the second form will have an outcome number = 2).
- **Item 4a1:** The C-section itself is not an Adverse Experience. If the C-section is performed due to or resulting from maternal complication(s), report each complication as an AE on an AE Log if the onset date is prior to termination. If a maternal complication AE meets the requirements for EAE reporting, complete an EAE Reporting form.
- **Items 4c–4f:** Refer to the protocol and applicable version of the *Manual for Expedited Reporting of Adverse Events to DAIDS* to evaluate if the outcome or any maternal complications, as a result of the pregnancy outcome, meets AE and/or EAE reporting requirements. If prior to study termination, a therapeutic/elective abortion is performed due to a pregnancy complication, the pregnancy complication should be reported on an Adverse Experience (AE) Log, with "procedure/surgery" marked under item 7, "Treatment."
- **Item 5:** Include information on medical conditions associated with the outcome, including early contractions, rupture of membranes, and cramping, along with actions taken as a result of these conditions.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐.☐ Outcome Number ☐

MTN007 (172) PO-2 (443)

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Pregnancy Outcome

☐ No data recorded on this page.

6. Were any fetal/infant congenital anomalies identified? ..... *yes* ☐ *no* ☐ *unknown* ☐

If no or unknown, go to item 7.

6a. Congenital anomalies identified. *Mark all that apply.* ***Complete AE Log and EAE Reporting form.***

- ☐ 6a1. Central nervous system, cranio-facial
- ☐ 6a2. Central nervous system, spinal
- ☐ 6a3. Cardiovascular
- ☐ 6a4. Renal
- ☐ 6a5. Gastrointestinal
- ☐ 6a6. Pulmonary
- ☐ 6a7. Musculoskeletal/extremities
- ☐ 6a8. Physical defect
- ☐ 6a9. Skin
- ☐ 6a10. Genitourinary
- ☐ 6a11. Chromosomal
- ☐ 6a12. Craniofacial (structural)
- ☐ 6a13. Hematologic
- ☐ 6a14. Infectious
- ☐ 6a15. Endocrine/metabolic
- ☐ 6a16. Other

6b. Describe the congenital anomaly/defect: _____

_____

Complete items 7–10 for live births only.

7. Infant gender: ..... *male* ☐ *female* ☐ *unknown* ☐

8. Infant birth weight: ..... ☐☐.☐ *kg* **OR** *unavailable* ☐

9. Infant gestational age by examination: ..... ☐☐ *weeks* ☐ *days* **OR** *unavailable* ☐ → *If unavailable, go to item 10.*

9a. Method used to determine gestational age: ..... *Ballard* ☐ *Dubowitz* ☐ *other, specify:* ☐ _____

10. Classification of the newborn by birth weight and gestational age (obstetric or by examination):

- ☐ Large for gestational age (> 90%)
- ☐ Appropriate for gestational age
- ☐ Small for gestational age (< 10%)
- ☐ Intrauterine growth retardation (< 3%)
- ☐ Classification not available

☐☐☐☒ 18-AUG-10

Language 01

Staff Initials / Date _____

Pregnancy Outcome (PO-2)

Item-specific Instructions:

- **Visit Code:** Record the visit code that is present on page 1 of this form.
- **No data recorded on this page:** This box must only be marked if all items on the page are left blank.
- **Outcome Number:** Record the outcome number that is present on page 1 of this form.
- **Item 6a:** If a woman on study has a baby with a congenital anomaly, report the event on an Adverse Experience (AE) Log, if prior to termination. On the AE Log, record "Congenital Anomaly in Offspring" on Item 1, record the Outcome Date as the Onset Date, and record the specific anomaly on the Comments line. Also submit an Expedited Adverse Event (EAE) Reporting form.
- **Items 7–10:** Complete these items for live birth outcomes only. If the outcome was stillbirth/intrauterine fetal demise, spontaneous abortion, ectopic pregnancy, therapeutic/elective abortion, or "other," leave items 7–10 blank and end the form (after item 6b).
- **Item 8:** Record the infant's birth weight as documented in medical records. If no medical record documentation of infant birth weight is available, complete this item based on participant report. Mark the "unavailable" box if no medical record documentation is available and the participant does not know the infant's birth weight.
- **Item 9:** If the infant's gestational age is determined using the Ballard method, please record "0" in the "days" box. Mark the "unavailable" box if no medical record documentation of the infant's gestational age is available.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) PR-1 (440)

Visit Code ☐.☐ 1

Participant ID

☐☐☐ - ☐☐☐☐☐ - ☐

Site Number Participant Number Chk

Pregnancy Report and History

PREGNANCY REPORT

		dd	MMM	yy
1.	First day of last menstrual period:	☐☐	☐☐☐	☐☐
2.	Estimated date of delivery:	☐☐	☐☐☐	☐☐

		yes	no
3.	What information was used to estimate the date of delivery?		
3a.	last menstrual period	☐	☐
3b.	initial ultrasound < 20 weeks	☐	☐
3c.	initial ultrasound ≥ 20 weeks	☐	☐
3d.	physical examination	☐	☐
3e.	conception date by assisted reproduction	☐	☐
3f.	other, specify: _____	☐	☐

PREGNANCY HISTORY

		yes	no
4.	Has the participant ever been pregnant before?	☐	☐ → ***If no, end of form.***
4a.	Is this the participant's first pregnancy since enrollment in this study?	☐	☐ → ***If no, go to item 5.***
4b.	Number of full term live births (≥ 37 weeks):	☐☐	
4c.	Number of premature live births (< 37 weeks):	☐☐	
4d.	Number of spontaneous fetal deaths and/or still births (≥ 20 weeks):	☐☐	
4e.	Number of spontaneous abortions (< 20 weeks):	☐☐	
4f.	Number of therapeutic/elective abortions:	☐☐	
4g.	Number of ectopic pregnancies:	☐☐	
5.	Does the participant have a history of pregnancy complications or fetal/infant congenital anomalies?	☐	☐ → ***If no, end of form.***
5a.	If yes, specify: _____		

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

0 1 Language

Staff Initials / Date

Pregnancy Report and History (PR-1)

Purpose: Complete this form when reporting a pregnancy of a study participant post enrollment through termination.

General Information/Instructions: A Pregnancy Report and History form is required for each new pregnancy that the participant experiences during the study.

- **Visit Code:** Record the visit code of the visit at which study staff became aware that the participant is/was pregnant.

Item-specific instructions:

- **Item 1**: A complete date is required. Record best estimate if date not known.
- **Item 2**: A complete date is required.
- **Item 3d**: Physical examination includes fundal height, uterine size by pelvic exam, and/or fetal heart rate.
- **Item 5**: Include information on pregnancy complications and fetal/infant congenital anomalies experienced prior to enrolling in the study as well as any conditions experienced/reported during the study.

SAMPLE: DO NOT FAX TO DATAFAX

Note: Number pages sequentially (01, 02, 03) for each participant. Page ☐☐

MTN007 (172) PH-1 (410)

Participant ID

☐☐☐ – ☐☐☐☐☐ – ☐

Site Number Participant Number Chk

Product Hold/Discontinuation Log

1. Date and visit code when study product hold was initiated: ☐☐ ☐☐☐ ☐☐ Visit Code ☐.☐
   dd MMM yy

2. Why is study product being held?

   ☐ pregnancy

   ☐ HIV positive result

   ☐ adverse experience → *AE Log page #* ☐☐☐

   ☐ other, specify: _____

3. Date of last study product use: ..... ☐☐ ☐☐☐ ☐☐
   dd MMM yy

4. Was the participant instructed to resume study product use? .....

	yes	*no (permanently discontinued)*	*no (hold continuing for another reason)*
	☐	☐	☐

In item 4a, record the date and visit code on which the participant would have been instructed to resume product use if not being held for another reason.

4a. Date and visit code when participant was instructed to resume or permanently discontinue study product use: ..... ☐☐ ☐☐☐ ☐☐ Visit Code ☐.☐
dd MMM yy

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

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Staff Initials / Date

Product Hold/Discontinuation Log (PH-1)

Purpose: This form is used to document temporary holds and early permanent discontinuations of study product use.

General Information/Instructions: This form is completed each time a participant is instructed to temporarily stop (hold) or permanently discontinue study product use prior to the Final Clinic Visit. If, at the same study visit, a product hold/discontinuation is initiated for more than one reason, complete a Product Hold/Discontinuation Log page for each reason. The same visit code should be used on each Log page.

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 1–3 have been completed. Refax the page once item 4 has been completed.

Item-specific Instructions:

- **Page:** Number pages sequentially throughout the study, starting with 01. Do not repeat page numbers. Do not renumber any Product Hold/Discontinuation Log pages after faxing, unless instructed by SCHARP.
- **Item 2:** Mark the box to the left of the reason why the participant is being instructed to hold or permanently discontinue study product use. If product is being held or discontinued due to an adverse experience, record the page number 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” box and record the reason for the hold/discontinuation on the line provided.
- **Item 3:** Record the date the participant last used study product. 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 product use or have determined that she is permanently discontinued from study product use. Mark this item “yes” if study staff instructed the participant that he/she can resume use of study product. If the participant was permanently discontinued from study product use, mark the “no (permanently discontinued)” box. 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).”
- **Item 4a:** Record the date and visit code on which the participant was told by a study staff member that he/she could resume or that she should permanently discontinue study product use. If “no (hold continuing for another reason)” is marked for item 4, in item 4a record the date and visit code that the participant would have been instructed to resume study product use based on resolution of the reason marked in item 2 of the form.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐.☐ 1

MTN007 (172) RE-1 (041)

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Rectal Exam

Exam Date

☐☐ ☐☐☐ ☐☐

dd *MMM* *yy*

PERIANAL VISUAL EXAMINATION

		normal findings	*abnormal findings*	*not done*	
1.	Findings from the perianal examination:	☐	☐	☐	***If normal findings or not done, go to item 2. If not done, specify reason in Comments.***

1a. Abnormal findings: *Mark all that apply.*

☐	Warts	☐	Leukoplakia
☐	Fissure	☐	Fistula
☐	Ulceration	☐	Petechiae (< 3 mm)
☐	Pigmentation	☐	Purpura (0.3–1 cm)
☐	Hemorrhoids	☐	Ecchymosis (> 1 cm)
☐	Skin tags	☐	Other abnormal findings, specify: _____

At Screening, evaluate any abnormalities for eligibility. At Enrollment, update Pre-exisiting Conditions form when applicable. During follow-up, complete or update Adverse Experience Log when applicable.

DIGITAL RECTAL EXAMINATION

		normal findings	*abnormal findings*	*not done*	
2.	Findings from the digital rectal examination:	☐	☐	☐	***If normal findings, end of form. If not done, specify reason in Comments.***

2a. Abnormal findings, specify: _____

At Screening, evaluate any abnormalities for eligibility. At Enrollment, update Pre-exisiting Conditions form when applicable. During follow-up, complete or update Adverse Experience Log when applicable.

Comments: _____

Rectal Exam (RE-1)

Purpose: This form is used to document the rectal exam findings (the perianal visual inspection as well as the digital rectal examination). A rectal exam is required at Screening, Enrollment, Treatment 1, and the Final Clinic Visit.

General Information/Instructions:

- **Visit Code:** Record the visit code assigned to this visit. Refer to the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.

Item-specific Instructions:

- **Item 1:** If the perianal visual examination was required but not done, mark the “not done” box and record the reason the visual examination was not done on the Comments lines.
- **Item 1a:** Mark the box to the left of each abnormal finding observed. If an observed abnormal finding is not listed, mark the “Other abnormal findings, specify” box and describe the abnormal finding on the line provided.
- **Item 2:** If a digital rectal examination was required but not done, mark the “not done” box and record the reason the digital rectal examination was not done on the Comments lines.
- **Item 2a:** If an abnormal finding is observed, record the finding(s) on the line provided.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) SC-1 (005)

Participant ID

Site Number – Participant Number – Chk

Screening Consent

Visit Date

dd MMM yy

		yes	no	
1.	Is the participant 18 years of age or older?	☐	☐ →	***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?	☐	☐ →	***If no, participant is ineligible. End of form.***

2a. When was the informed consent form for screening marked or signed? ..... dd MMM yy

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

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0 1 Language

Staff Initials / Date

Screening Consent (SC-1)

Purpose: 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 007 Participant ID.

General Information/Instructions: This form is faxed to SCHARP DataFax only if the participant enrolls in the study, and only after completion of his/her Enrollment Visit.

- **Visit Code:** There is no visit code field on this form because this form is only completed once at screening.
- ***Note**: If a participant is being re-screened, a new Screening Consent form must be completed as part of the subsequent screening attempt. See the Study-Specific Procedures (SSP) Manual for more instructions regarding re-screening, form completion and transmission procedures.*

Item-specific Instructions:

- **Item 1:** According to the protocol, a participant must be "≥ age of 18 at screening, verified per site SOP." Participants who are under 18 years should not be screened for the study.
- **Comments:** Record any necessary or additional information on the lines provided.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) SS-1 (161)

Visit Code ☐.☐ 1

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Specimen Storage

Initial Specimen Collection Date

☐☐ ☐☐☐ ☐☐

dd *MMM* *yy*

Alternate Collection Date

dd *MMM* *yy*

		not required	*stored*	*not stored*	*# specimens stored*
☐☐ ☐☐☐ ☐☐	1. Plasma archive	☐	☐	☐	
☐☐ ☐☐☐ ☐☐	2. Anorectal swabs for microflora	☐	☐	☐	
☐☐ ☐☐☐ ☐☐	3. Rectal sponge specimens.....	☐	☐	☐	
☐☐ ☐☐☐ ☐☐	4. Rectal lavage fluid.....	☐	☐	☐	
	5. Anoscopic biopsies				
☐☐ ☐☐☐ ☐☐	5a. histology.....	☐	☐	☐	☐
☐☐ ☐☐☐ ☐☐	5b. cytokine.....	☐	☐	☐	☐
☐☐ ☐☐☐ ☐☐	5c. phenotyping	☐	☐	☐	☐
☐☐ ☐☐☐ ☐☐	5d. gene expression	☐	☐	☐	☐
	6. Sigmoidoscopy biopsies				
☐☐ ☐☐☐ ☐☐	6a. histology.....	☐	☐	☐	☐
☐☐ ☐☐☐ ☐☐	6b. cytokine.....	☐	☐	☐	☐
☐☐ ☐☐☐ ☐☐	6c. phenotyping	☐	☐	☐	☐
☐☐ ☐☐☐ ☐☐	6d. gene expression	☐	☐	☐	☐

		not required	*collected*	*not collected*
☐☐ ☐☐☐ ☐☐	7. Fecal sample (calprotectin)	☐	☐	☐

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

0 1 Language

_____ Staff Initials / Date

Specimen Storage (SS-1)

Purpose: This form is used to document collection and storage of MTN 007 specimens that will be tested at a lab other than the local site laboratory.

General Information/Instructions: Check the information on this form against the MTN 007 LDMS Specimen Tracking Sheet completed for this visit to make sure the information is the same.

- **Visit Code:** Record the visit code assigned to the visit. Refer to the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **Initial Specimen Collection Date:** Record the date that the first specimen(s) was *collected* for this visit. A complete date is required.
- **Alternate Collection Date**: This date is to be completed ONLY if the specimen was collected after the Initial Specimen Collection Date for this same visit. Record a complete date.

Item-specific Instructions:

- **Items 1–6d**: If the specimen is not required to be collected and stored at this visit, mark the "not required" box. If the specimen is required to be stored, but for some reason it is not stored at this visit, mark the "not stored" box and record the reason why on the Comments line.
- **Items 5a–5d and 6a–6d:** If biopsies were stored, indicate the number of specimens stored in the space provided.
- **Item 7:** If the specimen is not required to be collected at this visit, mark the "not required" box. If the specimen is required to be collected, but for some reason it is not collected at this visit, mark the "not collected" box and record the reason why on the Comments line.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) STI-1 (131)

Visit Code ☐.☐ 1

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

STI Laboratory Results

Initial Specimen Collection Date

☐☐ ☐☐☐ ☐☐

dd *MMM* *yy*

1. HIV

Not done/ Not collected	Alternate Collection Date dd	MMM	yy		negative	positive	
☐	☐☐	☐☐☐	☐☐	1a. HIV EIA.....	☐	☐ →	***If positive, complete HIV Test Results form.***

2. SYPHILIS

Not done/ Not collected	dd	MMM	yy		non-reactive	reactive
☐	☐☐	☐☐☐	☐☐	2a. Syphilis RPR screening test	☐	☐
				If non-reactive, go to item 3. ←		
				2a1. Syphilis titer **1:**	☐☐☐☐	
					non-reactive	reactive
				2b. Syphilis confirmatory test	☐	☐

3. GC, CT, HSV

Not done/ Not collected	Alternate Collection Date dd	MMM	yy		negative	positive
☐	☐☐	☐☐☐	☐☐	3a. *N. gonorrhea* (urine)	☐	☐
☐	☐☐	☐☐☐	☐☐	3b. *C. trachomatis* (urine)	☐	☐
☐	☐☐	☐☐☐	☐☐	3c. *N. gonorrhea* (swab)	☐	☐
☐	☐☐	☐☐☐	☐☐	3d. *C. trachomatis* (swab)	☐	☐
☐	☐☐	☐☐☐	☐☐	3e. HSV-2	☐	☐
☐	☐☐	☐☐☐	☐☐	3f. HSV-1	☐	☐

4. HEPATITIS B

Not done/ Not collected	Alternate Collection Date dd	MMM	yy		non-reactive	reactive
☐	☐☐	☐☐☐	☐☐	4a. Hepatitis B (HBsAg) Surface Antigen	☐	☐

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

0 1 Language

Staff Initials / Date

STI Laboratory Results (STI-1)

Purpose: This form is used to document local STI laboratory results of specimens collected during screening, enrollment, and study follow-up.

General Information/Instructions: 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 (if ongoing at Enrollment), or an adverse experience on an Adverse Experience (AE) Log (for follow-up visit test result(s) only).

- **Visit Code:** Record the visit code assigned to the visit. Refer to the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.
- **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. Record a complete date.
- **Alternate Collection Date**: This date is to be completed ONLY if the specimen is collected after the Initial Specimen Collection Date for this same visit. Record a complete date.
- **Not Done/Not Collected:** For every test, mark *either* the "Not done/Not collected" box *or* enter a test result. If the "Not done/Not collected" box is marked, record reason on the Comments line.

Item-specific Instructions:

- **Item 1a:** Record the result of the non-rapid HIV EIA. If positive, complete the HIV Test Results form.
- **Item 2a:** If the syphilis screening test is reactive, items 2a1 and 2b must be completed.
- **Item 2a1:** 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."

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) SPR-1 (083)

Visit Code ☐.☐ 1

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Study Product Returns

		yes	no, specify:
1.	Was study product returned?	☐	☐ → ***End of form.***

2. Date product was returned by participant: ..... ☐☐ dd ☐☐☐ MMM ☐☐ yy

3. Number of **used** applicators returned: ..... ☐ ***used** applicators returned*

4. Number of **unused** applicators returned: ..... ☐ ***unused** applicators returned*

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

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01 Language

Staff Initials / Date

Study Product Returns (SPR-1)

Purpose: This form is used to document product returns.

General Information/Instructions: This form should be completed once for each participant after he/she has completed study treatment.

- **Visit Code:** Record the visit code assigned to the visit. Refer to the Study-Specific Procedures (SSP) Manual for more specific information on assigning visit codes.

Item-specific Instructions:

- **Item 1:** If study product was not returned, record the reason on the line provided.
- **Item 2:** Record the exact day, month, and year study product was returned by the participant.

SAMPLE: DO NOT FAX TO DATAFAX

MTN007 (172) 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. HIV tested **NOT APPLICABLE FOR THIS PROTOCOL.**
- ☐ 2i. inappropriate enrollment → ***End of form.***
- ☐ 2j. invalid ID due to duplicate screening/enrollment → ***End of form.***
- ☐ 2k. other, specify: _____
- ☐ 2l. early study closure → ***End of form.***

3. Was termination associated with an adverse experience? ..... *yes* ☐ *no* ☐ *don't know* ☐ → ***If no or don't know, end of form.***

3a. Record AE Log page: ___ ***OR*** Specify: _____

Comments: _____

☐ ☐ ☐ ☒ 04-SEP-09

0 1 Language

Staff Initials / Date

Termination (TM-1)

Purpose: This form should be 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.

General Information/Instructions: If a participant is terminated prior to completing all study product administration, complete a Product Hold/Discontinuation form.

Item-specific Instructions:

- **Item 1:** A complete date is required.
- **Item 2:** Mark only the primary reason for termination.
  - **Item 2a:** 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:** 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. If termination is associated with a non-reportable AE, record the event on the “specify” line.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number Participant Number Chk

Enrollment Visit Eligibility

Form Completion Date

[ ][ ] [ ][ ][ ] [ ][ ]

dd *MMM* *yy*

I now need to ask you one more question regarding your study participant. There is no right or wrong answer, so please be as honest and as accurate as you can.

1. Do you agree to not participant in any other trials involving drugs, medical devices, or genital products while you are on this study? .....

yes	*no*
☐	☐

If no, participant is ineligible.

End of interview.

2. *Within the past 12 months, did the participant report a history of excessive daily alcohol use (as defined by the CDC as heavy drinking consisting of an average consumption of more than 2 drinks per day for men, and more than 1 drink per day for women), frequent binge drinking, or illicit drug use that includes any injection drugs, methamphetamines (crystal meth), heroin, or cocaine, including crack cocaine? .....*

yes	*no*
☐	☐

If yes, participant is ineligible.

Enrollment Visit Eligibility (non-DataFax) - Page 1

Purpose: This form is used at the Enrollment Visit to document the participant's eligibility with regard to two eligibility criteria. This form is completed once, at the participant's Enrollment Visit.

General Information/Instructions: This is a mixed form—one item (item 1) is interviewer administered while item 2 is not. 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 Enrollment Visit Eligibility form must be completed as part of the subsequent screening attempt. See the Data Collection Section of the Study-Specific Procedures (SSP) Manual for more instructions regarding re-screening form completion procedures.*

MTN 007

LDMS Specimen Tracking Sheet

For login of MTN 007 stored specimens into LDMS

Participant ID	**Visit Code**	**Specimen Collection Date**
☐☐☐ - ☐☐☐☐☐ - ☐	☐.☐	☐☐ ☐☐☐ ☐☐
Site Number / Participant Number / Chk		*dd* / *MMM* / *yy*

# of TUBES or SPECIMENS	PRIMARY SPECIMEN	PRIMARY ADDITIVE	ALIQUOT DERIVATIVE	ALIQUOT SUB ADDITIVE/ DERIVATIVE	INSTRUCTIONS FOR PROCESSING LAB
☐	Blood – *Plasma* **(BLD)**	**EDT** (purple top)	**PL1**	**N/A**	Store in aliquots of 1-2 ml. If held at room temperature, plasma must be frozen within 4 hours of collection. If refrigerated or on ice, plasma must be frozen within 24 hours of collection.
☐	Rectal Swab – *Microflora* **(REC)**	**NON** (no additive)	**SWB**	**N/A**	Ship to NL on ice the day of collection
☐	Rectal Sponge – *Cytokines* **(REC)**	**PBS** (phosphate buffered saline)	**SPG**	**N/A**	Store @ <-70^{o}C within 4 hours of collection.
☐	Rectal Effluent – *Epithelial Sloughing* **(REC)**	**NOR**	**LAV**	**PFM**	Process and ship to NL the day of collection. Ship on ice. **Volume collected**: _____ mL
☐	Anoscopy Biopsies - *Histology* **(ARB)**	**FOR**	**TIS**	**N/A**	Ship to NL at room temperature the day of collection.
☐	Anoscopy Biopsies - *Cytokines* **(ARB)**	**RNL**	**TIS**	**N/A**	Store @ <-70^{o}C within 4 hours of collection. Specify cytokine test in specimen management. (See lab SSP section Table 12-4)

Comments: _____

_____

Initials: _____ (Sending Staff) _____ (Receiving Staff) **LDMS Data Entry Date:** ☐☐ *dd* ☐☐☐ *MMM* ☐☐ *yy* / _____ LDMS Staff

MTN 007 LDMS Specimen Tracking Sheet

For login of MTN 007 stored specimens into LDMS

MTN 007 LDMS Specimen Tracking Sheet (non-DataFax)

Purpose: This non-DataFax form is used to document collection and entry of MTN 007 specimens into the Laboratory Data Management System (LDMS).

General Information/Instructions: A copy of this form accompanies specimens for storage (in their original specimen collection containers) to the 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. Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Item-specific Instructions:

- **Visit Code:** Record the visit code of the visit at which the LMDS specimens were collected.
- **# of TUBES or SPECIMENS COLLECTED**: In the box provided, record the total number of tubes or specimens collected for that primary specimen type. 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 Data Entry Date – LDMS Staff:** The LDMS laboratory staff person who entered the specimens into LDMS, records his/her initials here.

MTN 007

LDMS Specimen Tracking Sheet

For login of MTN 007 stored specimens into LDMS

Participant ID	**Visit Code**	**Specimen Collection Date**
☐☐☐ - ☐☐☐☐☐ - ☐	☐.☐	☐☐ ☐☐☐ ☐☐
Site Number / Participant Number / Chk		*dd* / *MMM* / *yy*

# of TUBES or SPECIMENS	PRIMARY SPECIMEN	PRIMARY ADDITIVE	ALIQUOT DERIVATIVE	ALIQUOT SUB ADDITIVE/ DERIVATIVE	INSTRUCTIONS FOR PROCESSING LAB
☐	Anoscopy Biopsies - *Phenotyping* **(ARB)**	**RPM**	**TIS**	**N/A**	Ship to NL on ice the day of collection
☐	Anoscopy Biopsies - *Gene expression microarrays* **(ARB)**	**RNL**	**TIS**	**N/A**	Store @ 4°C overnight then transfer to -80°C. Must be stored at -80°C for a minimum of 24 hours prior to shipping. Specify Gene expression test in specimen management. (See lab SSP section Table 12-4)
☐	Sigmoidoscopy Biopsies - *Histology* **(FSR)**	**FOR**	**TIS**	**N/A**	Ship to NL the day of collection.
☐	Sigmoidoscopy Biopsies - *Cytokines* **(FSR)**	**RNL**	**TIS**	**N/A**	Store @ <-70°C within 4 hours of collection. Specify cytokine test in specimen management. (See lab SSP section Table 12-4)
☐	Sigmoidoscopy Biopsies - *Phenotyping* **(FSR)**	**RPM**	**TIS**	**N/A**	Ship to NL on ice the day of collection
☐	Sigmoidoscopy Biopsies - *Gene expression microarrays* **(FSR)**	**RNL**	**TIS**	**N/A**	Store @ 4°C overnight then transfer to -80°C. Must be stored at -80°C for a minimum of 24 hours prior to shipping. Specify Gene expression test in specimen management. (See lab SSP section Table 12-4)

Comments:_____

Initials: _____ (Sending Staff) _____ (Receiving Staff) **LDMS Data Entry Date:** ☐☐ ☐☐☐ ☐☐ / _____

dd *MMM* *yy* LDMS Staff

MTN 007 LDMS Specimen Tracking Sheet (non-DataFax)

Item-specific Instructions:

- **Visit Code:** Check to make sure the Visit Code recorded on page 1 and page 2 match.
- **NUMBER OF TUBES or SPECIMENS COLLECTED**: In the box provided, record the total number of tubes or specimens collected for that primary specimen type. 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 Data Entry Date – LDMS Staff:** The LDMS laboratory staff person who entered the specimens into LDMS, records his/her initials here.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number Participant Number Chk

Medical Eligibility

Form Completion Date

[ ][ ] [ ][ ][ ] [ ][ ]

dd *MMM* *yy*

1. At screening, did the participant report symptoms and/or have a clinical or laboratory diagnosis of any of the following active rectal or reproductive tract infections:

		yes	*no*	*N/A*
1a.	symptomatic urinary tract infection (UTI)?	☐	☐	
1b.	symptomatic bacterial vaginosis?	☐	☐	☐
1c.	symptomatic vaginal candidiasis?	☐	☐	☐
1d.	other vaginitis?	☐	☐	☐
1e.	trichomoniasis?	☐	☐	
1f.	chlamydia (CT)?	☐	☐	
1g.	gonorrhea (GC)?	☐	☐	
1h.	syphilis?	☐	☐	
1i.	active herpes (HSV) lesions?	☐	☐	
1j.	chancroid?	☐	☐	
1k.	pelvic inflammatory disease?	☐	☐	☐
1l.	genital sores or ulcers?	☐	☐	
1m.	cervicitis?	☐	☐	☐
1n.	symptomatic genital warts requiring treatment?	☐	☐	

Note: In cases of gonorrhea or Chlamydia identified at screening, one re-screening 2 months after the Screening Visit will be allowed.

If yes to any, participant is ineligible.

2. Answer the following questions based on the **participant's baseline medical history and screening rectal exam:**

		yes	*no*
2a.	Does the participant have any abnormalities of the colorectal mucosa, or significant colorectal symptoms(s), which, in the opinion of the clinician, represents a contraindication to biopsy (including but not limited to presence of any unresolved injury, infectious or inflammatory condition of the local mucosa, and presence of symptomatic external hemorrhoids)?	☐	☐
2b.	Has the participant had an anorectal STI within 6 months prior to the Screening Visit?	☐	☐
2c.	Does the participant have a history of significant gastrointestinal bleeding in the opinion of the investigator?	☐	☐
2d.	Is the participant allergic to methylparaben, propylparaben, sorbic acid, and components of N-9?	☐	☐

If yes to any, participant is ineligible.

Medical Eligibility (non-DataFax) - Page 1

Purpose: This form is used to document the participant's medical eligibility for the study. This form is completed based on review of all clinical and lab test results documentation from the participant's Screening and Enrollment Visits.

General Information/Instructions: 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 Medical Eligibility form must be completed as part of the subsequent screening attempt. See the Study-Specific Procedures (SSP) Manual for more instructions regarding re-screening form completion procedures.*

Item-specific Instructions:

- **Items 1a–1n:** Per the protocol, anyone diagnosed with an active rectal or reproductive track infection or urinary tract infection at screening is ineligible for the study. However, in cases of gonorrhea or Chlamydia identified at screening, one re-screening 2 months after the initial screening visit is allowed.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Medical Eligibility

		yes	no
2e.	Does the participant have a history of recurrent urticaria?	☐	☐
2f.	Does the participant have a history of bleeding problems?	☐	☐

If yes, participant is ineligible.

3. Answer the following questions based on the **participant's screening laboratory results:**

		yes	no
3a.	Is the participant HIV-1 uninfected according to the standard DAIDS algorithm in Appendix II of the protocol?	☐	☐
3b.	Did the participant test positive for Hepatitis B surface antigen (HBsAg)?	☐	☐
3c.	Is the participant's hemoglobin less than 10.0 g/dL?	☐	☐
3d.	Is the participant's platelet count less than 100,000/mm^3?	☐	☐
3e.	If the participant's white blood count less than 2000 cells/mm^3 or greater than 15,000 cells/mm^3?	☐	☐
3f.	Is the participant's calculated creatinine clearance less than 60 mL/min? ***Note: remember to use female- and male-specific formulas when calculating creatinine clearance.***	☐	☐
3g.	Is the participant's serum creatinine greater than 1.3 times the site laboratory upper limit of normal (ULN)?	☐	☐
3h.	Is the participant's ALT and/or AST greater than 2.5 times the site laboratory ULN?	☐	☐
3i.	Did the participant have a urinalysis glucose result of +1 or a urinalysis protein result of +1?	☐	☐

If no, participant is ineligible.

If yes to any, participant is ineligible.

Medical Eligibility (non-DataFax) - Page 2

No additional instructions.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

☐☐☐ – ☐☐☐☐☐ – ☐

Site Number Participant Number Chk

Medical Eligibility

		yes	no	
4.	Is the participant in general good health?	☐	☐ →	***If no, participant is ineligible.***
5.	Does the participant have any other condition or prior therapy that, in the opinion of the investigator, would preclude informed consent, make study participation unsafe, or make the individual unsuitable for the study or unable to comply with the study requirements? Such conditions may include, but are not limited to, current or recent history of severe, progressive, or uncontrolled substance abuse, or renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, or cerebral disease.	☐	☐	***If yes, participant is ineligible.***

For female participants of childbearing potential only.

		negative	positive	
6.	hCG pregnancy test result (at the Enrollment/ Baseline Visit):	☐	☐ →	***If positive, participant is ineligible.***

Medical Eligibility (non-DataFax) - Page 3

No additional instructions.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

Site Number – Participant Number – Chk

Participant-reported Baseline Medical and Menstrual History

Visit Date dd MMM yy

	Medical problem? yes	no	*If yes, date diagnosed:* MMM	yy	***Description***	***Ongoing?*** yes	no	***Severity Grade***
HE (head/eyes)	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	
ENT (ears/ nose/throat)	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	
Lymphatic	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	
Cardiovascular	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	
Respiratory	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	
Liver	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	

If yes to any, evaluate for eligibility.
If yes to any at time of Enrollment, record on Pre-existing Conditions form.

☐ ☐ ☐ ☒ 04-SEP-09

0 1 Language

Staff Initials / Date

Participant-reported Baseline Medical and Menstrual History (non-DataFax) - Page 1

Purpose: This form is used to document a participant's baseline medical history since becoming sexually active (i.e., age at first act of anal or vaginal intercourse). It is first completed at the Screening Visit. It is then updated at any subsequent visits related to the same screening attempt, and updated again at the Enrollment Visit.

General Information/Instructions:

- 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 the Study-Specific Procedures Manual (SSP) 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 his or her medical history at baseline. Record all conditions that were ongoing at enrollment on the Pre-existing Conditions form.*

Item-specific Instructions:

- **Medical problem:** For each organ system/disease listed, mark the "yes" 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 "no" box for conditions not reported or documented in medical records.
- **If yes, date diagnosed:** For each organ system/disease marked "yes," record the month and year the participant was diagnosed with the condition or began experiencing symptoms.
- **Ongoing:** For each diagnosed or reported condition, determine if it 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.
- **Severity Grade:** Assign a severity grade to all diagnosed conditions that are ongoing. To grade the severity, consult the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies)*, as appropriate. AEs not included in those tables will be graded by the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences*. If a condition is not gradable, write "NG."

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

[ ][ ][ ] - [ ][ ][ ][ ][ ] - [ ]

Site Number | Participant Number | Chk

Participant-reported Baseline Medical and Menstrual History

	Medical problem?		*If yes, date diagnosed:*		***Description***	***Ongoing?***		***Severity Grade***
	yes	*no*	*MMM*	*yy*		*yes*	*no*	
Renal *(including urinary symptoms)*	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	
Musculoskeletal	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	
Neurologic	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	
Skin	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	
Endocrine/ Metabolic	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	
Hematologic	☐	☐				☐	☐	
	☐	☐				☐	☐	
	☐	☐				☐	☐	

If yes to any, evaluate for eligibility.
If yes to any at time of Enrollment, record on Pre-existing Conditions form.

☐ ☐ ☐ ☒ 04-SEP-09

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Language

Staff Initials / Date

Participant-reported Baseline Medical and Menstrual History (non-DataFax) - Page 2

Item-specific Instructions:

- **Medical problem:** For each organ system/disease listed, mark the "yes" 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 "no" box for conditions not reported or documented in medical records.
- **If yes, date diagnosed:** For each organ system/disease marked "yes," record the month and year the participant was diagnosed with the condition or began experiencing symptoms.
- **Ongoing:** For each diagnosed or reported condition, determine if it 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.
- **Severity Grade:** Assign a severity grade to all diagnosed conditions that are ongoing. To grade the severity, consult the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies)*, as appropriate. AEs not included in those tables will be graded by the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences*. If a condition is not gradable, write "NG."

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number | Participant Number | Chk

Participant-reported Baseline Medical and Menstrual History

	Medical problem?		***If yes, date diagnosed:***		***Description***	***Ongoing?***		***Severity Grade***
	yes	*no*	*MMM*	*yy*		*yes*	*no*	
Cancer	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
Drug Allergy	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
Other Allergy *(including components of N-9)*	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
Mental Illness	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____
	☐	☐	☐☐☐	☐☐	_____	☐	☐	_____

If yes to any, evaluate for eligibility.
If yes to any at time of Enrollment, record on Pre-existing Conditions form.

Participant-reported Baseline Medical and Menstrual History (non-DataFax) - Page 3

Item-specific Instructions:

- **Medical problem:** For each organ system/disease listed, mark the "yes" 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 "no" box for conditions not reported or documented in medical records.
- **If yes, date diagnosed:** For each organ system/disease marked "yes," record the month and year the participant was diagnosed with the condition or began experiencing symptoms.
- **Ongoing:** For each diagnosed or reported condition, determine if it 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.
- **Severity Grade:** Assign a severity grade to all diagnosed conditions that are ongoing. To grade the severity, consult the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies)*, as appropriate. AEs not included in those tables will be graded by the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences*. If a condition is not gradable, write "NG."

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number | Participant Number | Chk

Participant-reported Baseline Medical and Menstrual History

	Description	*Ongoing?* yes	no	*Severity Grade*
History of Alcohol Use:	______	☐	☐	______
History of Recreational Drug Use:	______	☐	☐	______

	Medical problem? yes	no	*If yes, date diagnosed:* MMM	yy	*Description*	*Ongoing?* yes	no	*Severity Grade*
STI/RTI	☐	☐	☐☐☐	☐☐	______	☐	☐	______

☐ symptomatic vaginal candidiasis ☐ HSV-1/HSV-2 ☐ HPV/warts ☐ cervicitis
☐ abnormal Pap ☐ Syphilis ☐ Trichomoniasis ☐ other
☐ symptomatic BV ☐ Gonorrhea ☐ other vaginitis
☐ PID ☐ Chlamydia ☐ chancroid

STI/RTI	☐	☐	☐☐☐	☐☐	______	☐	☐	______

☐ symptomatic vaginal candidiasis ☐ HSV-1/HSV-2 ☐ HPV/warts ☐ cervicitis
☐ abnormal Pap ☐ Syphilis ☐ Trichomoniasis ☐ other
☐ symptomatic BV ☐ Gonorrhea ☐ other vaginitis
☐ PID ☐ Chlamydia ☐ chancroid

STI/RTI	☐	☐	☐☐☐	☐☐	______	☐	☐	______

☐ symptomatic vaginal candidiasis ☐ HSV-1/HSV-2 ☐ HPV/warts ☐ cervicitis
☐ abnormal Pap ☐ Syphilis ☐ Trichomoniasis ☐ other
☐ symptomatic BV ☐ Gonorrhea ☐ other vaginitis
☐ PID ☐ Chlamydia ☐ chancroid

If yes to any, evaluate for eligibility.
If yes to any at time of Enrollment, record on Pre-existing Conditions form.

Participant-reported Baseline Medical and Menstrual History (non-DataFax) - Page 4

Item-specific Instructions:

- **Medical problem:** Mark the "yes" box for each STI/RTI (evidenced by participant report or by medical records) that the participant has ever experienced since becoming sexually active, if any. For each STI/RTI reported, mark the box that corresponds to the specific STI/RTI the participant experienced (e.g., "Gonorrhea"). Mark the "no" box for the remaining STI/RTI items.
- **If yes, date diagnosed:** For each item marked "yes," record the month and year the participant was diagnosed with the condition or began experiencing symptoms.
- **Ongoing:** For each diagnosed or reported condition, determine if it 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.
- **Severity Grade:** Assign a severity grade to all diagnosed conditions that are ongoing. To grade the severity, consult the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies)*, as appropriate. AEs not included in those tables will be graded by the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences*. If a condition is not gradable, write "NG."

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

Site Number – Participant Number – Chk

Participant-reported Baseline Medical and Menstrual History

Anal/Colorectal/GI Symptoms

	Medical problem?		*If yes, date diagnosed:*		***Description***	***Ongoing?***		***Severity Grade***
	yes	*no*	*MMM*	*yy*		*yes*	*no*	
Constipation?	☐	☐				☐	☐	
Pain during defecation?	☐	☐				☐	☐	
Diarrhea?	☐	☐				☐	☐	
Urgency?	☐	☐				☐	☐	
Fecal incontinence?	☐	☐				☐	☐	
Abdominal distension or bloating?	☐	☐				☐	☐	
Flatulence?	☐	☐				☐	☐	
Anorectal discharge?	☐	☐				☐	☐	
Anal pain?	☐	☐				☐	☐	
Rectal pain?	☐	☐				☐	☐	
Abdominal pain?	☐	☐				☐	☐	
Perineal pain?	☐	☐				☐	☐	
Rectal/anal bleeding?	☐	☐				☐	☐	
Bloody stools?	☐	☐				☐	☐	
Bloody diarrhea?	☐	☐				☐	☐	
Black, tarry stools?	☐	☐				☐	☐	
Perianal itching?	☐	☐				☐	☐	
Perianal discomfort?	☐	☐				☐	☐	
Perianal mass or lump?	☐	☐				☐	☐	

If yes to any, evaluate for eligibility.
If yes to any at time of Enrollment, record on Pre-existing Conditions form.

Participant-reported Baseline Medical and Menstrual History (non-DataFax) - Page 5

Item-specific Instructions:

- **Anal/Colorectal/GI Symptoms:** These questions refer to any anal/colorectal/GI symptoms the participant may have experienced since becoming sexually active. For each item marked "yes," complete the adjacent items. For items marked "no," leave the adjacent items blank. For any item marked "yes," provide treatment as necessary.
- **If yes, date diagnosed:** For each item marked "yes," record the month and year the participant was diagnosed with the condition or began experiencing symptoms.
- **Ongoing:** For each reported symptom or condition, determine if it is ongoing or resolved. Review all ongoing symptoms/conditions at the participant's Enrollment Visit and determine eligibility. For symptoms/conditions ongoing at Enrollment, record the condition on the participant's Pre-existing Conditions form.
- **Severity Grade:** Assign a severity grade to all diagnosed conditions that are ongoing. To grade the severity, consult the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies)*, as appropriate. AEs not included in those tables will be graded by the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences*. If a condition is not gradable, write "NG."

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

[ ][ ][ ] - [ ][ ][ ][ ][ ] - [ ]

Site Number | Participant Number | Chk

Participant-reported Baseline Medical and Menstrual History

	Medical problem? *yes*	*no*	*If yes, date diagnosed: MMM*	*yy*	***Description***	***Ongoing?*** *yes*	*no*	***Severity Grade***
Hemorrhoids?	☐	☐	☐☐☐	☐☐		☐	☐	
Anal warts?	☐	☐	☐☐☐	☐☐		☐	☐	
Nausea?	☐	☐	☐☐☐	☐☐		☐	☐	
Vomiting?	☐	☐	☐☐☐	☐☐		☐	☐	
Weight loss?	☐	☐	☐☐☐	☐☐		☐	☐	
Other, specify? _____	☐	☐	☐☐☐	☐☐		☐	☐	

If yes to any, evaluate for eligibility.
If yes to any at time of Enrollment, record on Pre-existing Conditions form.

Other medical problem?	*yes*	*no*	*If yes, date diagnosed: MMM*	*yy*	***Description***	***Ongoing?*** *yes*	*no*	***Severity Grade***
Other?	☐	☐	☐☐☐	☐☐		☐	☐	
Other?	☐	☐	☐☐☐	☐☐		☐	☐	

If yes to any, evaluate for eligibility.
If yes to any at time of Enrollment, record on Pre-existing Conditions form.

History of sexual assault (if any): _____

History of any other obstetric (women only), gynecologic (women only), or reproductive problems, and/or procedures not recorded elsewhere on this form (record severity grade, if ongoing):

Male participants, end of form.

Participant-reported Baseline Medical and Menstrual History (non-DataFax) - Page 6

Item-specific Instructions:

- **Other Medical Problem:** Record any symptom or condition reported by the participant that is not recorded elsewhere on this form.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number | Participant Number | Chk

Women Only: Participant-reported Baseline Medical and Menstrual History

Menstrual History

	dd	*MMM*	*yy*
First day of last menstrual period:	[ ][ ]	[ ][ ][ ]	[ ][ ]
Last day of last menstrual period:	[ ][ ]	[ ][ ][ ]	[ ][ ]

If participant's last menstrual period was more than one month ago, record relevant clinical history (include severity grade, if missed menses is unexpected).

_____

_____

	regular	*irregular*
Usual menstrual cycle:	☐	☐

Usual number of days between menses: ..... [ ][ ] *# of days*

	minimum		*maximum*	
Usual number of bleeding days (record range):	[ ][ ]	*# of days*	***TO*** [ ][ ]	*# of days*

Age of menarche: ..... [ ][ ] *years*

	light	*moderate*	*heavy*
Usual type of menstrual flow (at the heaviest day of menses):	☐	☐	☐

Usual menstrual symptoms (document start date, type and severity, if any): _____

_____

Usual non-menstrual genital bleeding pattern (document start date, frequency, duration, type of flow, and associated symptoms, if any):

_____

History of any other menstrual problems not recorded above (record severity grade, if ongoing):

_____

_____

_____

Participant-reported Baseline Medical and Menstrual History (non-DataFax) - Page 7

These questions are for women only.

Item-specific Instructions:

- **First/Last day of last menstrual period:** Record the dates relating to the participant's most recently completed menses regardless of how long ago it occurred. At minimum, month and year are required.
- **Usual number of days between menses:** If the participant is amenorrheic, refer to her previous menstrual cycles that occurred prior to the amenorrhea.
- **Usual number of bleeding days:** If the participant is amenorrheic, refer to her previous menstrual cycles that occurred prior to the amenorrhea.
- **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.

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MTN007 (172)

Participant ID

[ ][ ][ ] - [ ][ ][ ][ ][ ] - [ ]

Site Number Participant Number Chk

Women Only: Participant-reported Baseline Medical and Menstrual History

Pregnancy History

Preg #	Outcome Date	Outcome *(fullterm, preterm, ectopic, SAB, TAB, etc.)*	Type of Delivery *(vag, cesarean, D&C)*	Alive now?	Congenital anomalies or problems with pregnancy *(describe)*
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					

Contraceptive History

Current Method(s)	Approx. Dates of Use	Any problems?
Previously Used Method(s)	**Approx. Dates of Use**	**Any problems?**

Note: To be eligible for study participation, participant must report at enrollment use of an effective method of contraception (e.g., barrier method, IUD, hormonal contraception, surgical sterilization, or vasectomization of male partner). If the female participant has female partners only, note the method of contraception as a barrier method in the study documentation.

[ ][ ][ ][X] 04-SEP-09

[0][1] Language

Staff Initials / Date

Participant-reported Baseline Medical and Menstrual History (non-DataFax) - Page 8

These questions are for women only.

Item-specific Instructions:

- **Pregnancy History:** Record the outcome date, outcome (for example, full-term live birth, premature live birth, spontaneous abortion, etc.) and other relevant information regarding each of the participant's pregnancies.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

Site Number – Participant Number – Chk

Participant-reported Follow-up Medical and Menstrual History

Visit Date dd MMM yy

	Medical problem since last visit? yes	no	***If yes, onset date:*** dd	MMM	OR yy	***continuing from previous visit***	***Description*** *(include severity grade and outcome date, if applicable)*
HE (head/eyes)	☐	☐	☐☐	☐☐☐	☐☐	☐	
	☐	☐	☐☐	☐☐☐	☐☐	☐	
ENT (ears/ nose/throat)	☐	☐	☐☐	☐☐☐	☐☐	☐	
	☐	☐	☐☐	☐☐☐	☐☐	☐	
Lymphatic	☐	☐	☐☐	☐☐☐	☐☐	☐	
	☐	☐	☐☐	☐☐☐	☐☐	☐	
Cardiovascular	☐	☐	☐☐	☐☐☐	☐☐	☐	
	☐	☐	☐☐	☐☐☐	☐☐	☐	
Respiratory	☐	☐	☐☐	☐☐☐	☐☐	☐	
	☐	☐	☐☐	☐☐☐	☐☐	☐	
Liver	☐	☐	☐☐	☐☐☐	☐☐	☐	
	☐	☐	☐☐	☐☐☐	☐☐	☐	
Renal *(including urinary symptoms)*	☐	☐	☐☐	☐☐☐	☐☐	☐	
	☐	☐	☐☐	☐☐☐	☐☐	☐	
Musculoskeletal	☐	☐	☐☐	☐☐☐	☐☐	☐	
	☐	☐	☐☐	☐☐☐	☐☐	☐	

Update or complete Adverse Experience Log when applicable.

Participant-reported Follow-up Medical and Menstrual History (non-DataFax) - Page 1

Purpose: This form is used to document a participant's follow-up medical history during the study (that is, his/her medical history since his/her last study visit). It is completed at each regularly scheduled follow-up visit.

General Information/Instructions:

- It may be helpful to use a calendar as a probe to help participants recall dates.
- Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.
- ***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 his/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:

- **Yes/No boxes:** The first time this form is completed for a participant (at his/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 yes, onset date:** For each item marked "yes," record the day, month, and year the participant was diagnosed with the condition. When applicable, complete an Adverse Experience Log form 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 yes, onset date" boxes blank. If an onset date is recorded, leave the "continuing from previous visit" box blank.
- **Update or complete Adverse Experience Log when applicable:** For each item diagnosed, complete an Adverse Experience Log form (if applicable) 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 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 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—do record on this form that the condition has not increased in severity or frequency since enrollment/baseline.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

Site Number – Participant Number – Chk

Participant-reported Follow-up Medical and Menstrual History

	Medical problem since last visit? *yes*	*no*	***If yes, onset date:*** *dd* *MMM* *yy*	***OR continuing from previous visit***	***Description*** *(include severity grade and outcome date, if applicable)*
Neurologic	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
Skin	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
Endocrine/ Metabolic	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
Hematologic	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
Cancer	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
Drug Allergy	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
Other Allergy	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
Mental Illness	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐
	☐	☐	☐☐ ☐☐☐ ☐☐	☐☐	☐

Update or complete Adverse Experience Log when applicable.

Any changes in alcohol use since last study visit?

Any changes in recreational drug use since last study visit?

Participant-reported Follow-up Medical and Menstrual History (non-DataFax) - Page 2

Item-specific Instructions:

- **Yes/No boxes:** The first time this form is completed for a participant (at his/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 yes, onset date:** For each item marked "yes," record the day, month, and year the participant was diagnosed with the condition. When applicable, complete an Adverse Experience Log form 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 yes, onset date" boxes blank. If an onset date is recorded, leave the "continuing from previous visit" box blank.
- **Update or complete Adverse Experience Log when applicable:** For each item diagnosed, complete an Adverse Experience Log form (if applicable) 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 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 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—do record on this form that the condition has not increased in severity or frequency since enrollment/baseline.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

Site Number – Participant Number – Chk

Participant-reported Follow-up Medical and Menstrual History

Since his or her last study visit, has the participant experienced any of the following symptoms:

Anal/Colorectal/GI Symptoms	*yes*	*no*	***If yes, onset date:*** *dd*	*MMM*	*yy*	***OR continuing from previous visit***	***Description*** *(include severity grade and outcome date, if applicable)*
Constipation?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Pain during defecation?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Diarrhea?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Urgency?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Fecal incontinence?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Abdominal distension or bloating?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Flatulence?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Anorectal discharge?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Anal pain?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Rectal pain	☐	☐	☐☐	☐☐☐	☐☐	☐	
Abdominal pain?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Perineal pain?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Rectal/anal bleeding?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Bloody stools?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Bloody diarrhea?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Black, tarry stools?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Perianal itching?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Perianal discomfort?	☐	☐	☐☐	☐☐☐	☐☐	☐	
Perianal mass or lump?	☐	☐	☐☐	☐☐☐	☐☐	☐	

If yes to any, conduct rectal exam if clinically indicated. Update or complete Adverse Experience Log when applicable.

Participant-reported Follow-up Medical and Menstrual History (non-DataFax) - Page 3

Item-specific Instructions:

- **Anal/Colorectal/GI Symptoms:** For any item marked "yes," conduct a rectal exam if clinically indicated (and not already required for the visit). Provide treatment as necessary.
- **If yes, onset date:** For each item marked "yes," record the day, month, and year the participant was diagnosed with the condition or began experiencing symptoms. When applicable, complete an Adverse Experience Log form 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 symptom or condition is recorded on a previously-completed medical history form). If this box is marked, leave the "If yes, onset date" boxes blank. If an onset date is recorded, leave the "continuing from previous visit" box blank.
- **Update or complete Adverse Experience Log when applicable:** For each item, complete an Adverse Experience Log form (if applicable) if this is the **first time** the symptom or condition has been reported since the participant enrolled in the study. If this is **not** the first time the symptom/condition has been reported since enrollment, an AE Log should already have been completed for this symptom/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/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—do record on this form that the condition has not increased in severity or frequency since enrollment/baseline.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

Site Number – Participant Number – Chk

Participant-reported Follow-up Medical and Menstrual History

	Medical problem since last visit? *yes*	*no*	***If yes, onset date:*** *dd*	*MMM*	*yy*	***OR continuing from previous visit***	***Description*** *(include severity grade and outcome date, if applicable)*
Hemorrhoids?	☐	☐				☐	
Anal warts?	☐	☐				☐	
Nausea?	☐	☐				☐	
Vomiting?	☐	☐				☐	
Weight loss?	☐	☐				☐	
Other, specify? _____	☐	☐				☐	

→ *If yes to any, conduct rectal exam if clinically indicated. Update or complete Adverse Experience Log when applicable.*

Other medical problem since last visit?	*yes*	*no*	***If yes, onset date:*** *dd*	*MMM*	*yy*	***OR continuing from previous visit***	***Description*** *(include severity grade and outcome date, if applicable)*
Other?	☐	☐				☐	
Other?	☐	☐				☐	

→ *Update or complete Adverse Experience Log when applicable.*

Any changes to obstetric/gynecologic/reproductive history since last study visit? ..... *yes* ☐ *no* ☐

→ ***If yes, specify below.***

_____

_____

_____

_____

_____

_____

Male participants, end of form.

☐ ☐ ☐ ☒ 04-SEP-09

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0 1 Language

Staff Initials / Date

Participant-reported Follow-up Medical and Menstrual History (non-DataFax) - Page 4

Item-specific Instructions:

- **Other Medical Problems since last visit:** Record any symptom or condition reported by the participant that is not recorded elsewhere on this form.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

			–						–	

Site Number Participant Number Chk

Women Only: Participant-reported Follow-up Medical and Menstrual History

Menstrual Information

First day of last menstrual period: ..... dd MMM yy

Last day of last menstrual period: ..... dd MMM yy

no menses since last visit **OR** ☐

If no menses since last visit, is it unexpected or unexplained? ..... ☐ yes ☐ no

If yes, document Severity Grade here:_____
and complete Adverse Experience Log, when applicable.

Any changes to contraception/family planning use not recorded elsewhere on this form? ..... ☐ yes ☐ no

If yes, specify below. Include start and stop dates. Update Concomitant Medications Log when applicable.

Additional Notes: _____

Participant-reported Follow-up Medical and Menstrual History (non-DataFax) - Page 5

These questions are for women only.

Item-specific Instructions:

- **No menses since last visit:** If the participant has not had a menstrual period since her last study visit, mark this box and leave the date boxes (ddMMMyy) blank for First and Last day of last menstrual period.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID ☐☐☐-☐☐☐☐☐-☐
Site Number / Participant Number / Chk

Physical Exam

Exam Date ☐☐/☐☐☐/☐☐
dd *MMM* *yy*

VITAL SIGNS

1. Were vital signs done? ☐ *yes* ☐ *no* → ***If no, specify reason:*** ______________________

Weight ☐☐☐ *kg* BP ☐☐☐ / ☐☐☐ *mmHg*

Height ☐☐☐ *cm* Pulse ☐☐☐ *beats per minute*

Oral Temp ☐☐.☐ *°C*

______ Vital Signs: Staff Initials / Date

FINDINGS

Items 2 and 3 are required. If not evaluated or abnormal, please specify.

not evaluated	*normal*	*abnormal*	
☐	☐	☐	2. General appearance ______________________
☐	☐	☐	3. Abdomen ______________________

Items 4–15 are optional. If abnormal, please specify.

not evaluated	*normal*	*abnormal*	
☐	☐	☐	4. HEENT ______________________ ______________________
☐	☐	☐	5. Lymph Nodes ______________________
☐	☐	☐	6. Neck ______________________
☐	☐	☐	7. Heart ______________________
☐	☐	☐	8. Lungs ______________________
☐	☐	☐	9. Breast Exam ______________________
☐	☐	☐	10. Extremities ______________________
☐	☐	☐	11. Skin ______________________
☐	☐	☐	12. Neurological ______________________
☐	☐	☐	13. Musculoskeletal (including bone fractures) ______________________
☐	☐	☐	14. Other, specify ______________________
☐	☐	☐	15. Other, specify ______________________

→ ***If abnormal at Screening, evaluate for eligibility.***
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

Physical Exam (non-DataFax) - Page 1

Purpose: This form is used to document the participant's vital signs and physical exam findings at screening and during study follow-up.

General Information/Instructions: Because this form is a non-DataFax form, this form should NOT be faxed to SCHARP DataFax.

Item-specific Instructions:

- **Vital Signs:** Remember to use leading zeros when needed and round to the nearest whole number. The staff member who completes these items should initial and date on the line provided.
- **Findings:** The staff member who completes these items should initial and date on the line provided.
- **Items 14–15:** Use these items to list any additional organ systems that were evaluated. If no other organ systems other than the ones listed in items 2–13 were evaluated, mark these items as "not evaluated."

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number Participant Number Chk

Screening Visit Eligibility

Form Completion Date

[ ][ ] [ ][ ][ ] [ ][ ]

dd *MMM* *yy*

I am now going to ask some questions about you, your sexual behaviors, and your health. There are no right or wrong answers, so please be as honest and as accurate as you can. Some of the questions may seem personal, but please remember that all of your answers will be kept confidential.

		yes	no	
1.	For this study, are you wiling and able to communicate in English?	☐	☐	
2.	Are you available to return for all study visits, barring any unforeseen circumstances?	☐	☐	
3.	Have you had consensual receptive anal intercourse at least once in the last year?	☐	☐	
4.	Are you willing to abstain from receptive anal intercourse for the duration of study participation (approximately 4–8 weeks)?	☐	☐	
5.	Are you willing to abstain from insertion of anything rectally, including sex toys, other than study gel, for the duration of study participation (approximately 4–8 weeks)?	☐	☐	
6.	Do you agree to use study-provided condoms for the duration of the study for vaginal and insertive anal intercourse?	☐	☐	
7.	Do you agree not to participate in any other trials involving drugs, medical devices, or genital products while you are in this study?	☐	☐	***If no to any, participant is ineligible.***
		yes	*no*	
8.	Do you have any known HIV-infected partners?	☐	☐	***If yes, participant is ineligible.***
9.	Do you anticipate that you will use any of the following medications during the period of study participation:	*yes*	*no*	
9a.	Heparin, including Lovenox?	☐	☐	*Interviewer: Provide examples of medicines, if needed.*
9b.	Warfarin?	☐	☐	
9c.	Plavix (clopidogrel bisulfate)?	☐	☐	
9d.	Rectally administered medications (including over-the-counter products)?	☐	☐	
9e.	Aspirin?	☐	☐	
9f.	Non-steroidal anti-inflammatory drugs (NSAIDS)?	☐	☐	***If yes to any, participant must be willing to abstain from use during study participation.***
9g.	Any other drugs that are associated with increased likelihood of bleeding following mucosal biopsy?	☐	☐	

[0][1] Language

Staff Initials / Date

Screening Visit Eligibility (non-DataFax) - Page 1

Purpose: This form is used to document the participant's eligibility at the Screening Visit.

General Information/Instructions: This is a mixed form—some of the items (items 1–16) are interviewer administered while some of the items (items 17–18) are not. 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 Visit Eligibility form must be completed as part of the subsequent screening attempt. See the Data Collection Section of the Study-Specific Procedures (SSP) Manual for more instructions regarding re-screening form completion procedures.*

Item-specific Instructions:

- **Items 1–16:** If the participant provides a response indicating that he/she is ineligible for the study, continue to administer this form through item 16. Do not inform him/her that he/she is ineligible for the study until the form has been completely administered. Also, refrain from indicating to the participant the reason why he/she is ineligible, to prevent socially desirable reporting.
- **Items 9a–9f:** If the participant is unfamiliar with any medications listed, provide specific examples. For example, if a participant does not know what a non-steroidal anti-inflammatory drug (NSAID) is the interviewer could say, "for example, ibuprofen (such as Advil or Motrin) or naproxen (such as Aleve)." Any example of a NSAID is fine to mention.
- **Item 9g:** Please provide examples of medicines for this item.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number Participant Number Chk

Screening Visit Eligibility

10. Would you be willing to abstain from the following medications during the period of study participation:

	yes	no
10a. Heparin, including Lovenox?	☐	☐
10b. Warfarin?	☐	☐
10c. Plavix (clopidogrel bisulfate)?	☐	☐
10d. Rectally administered medications (including over-the-counter products)?	☐	☐
10e. Aspirin?	☐	☐
10f. Non-steroidal anti-inflammatory drugs (NSAIDS)?	☐	☐
10g. Any other drugs that are associated with increased likelihood of bleeding following mucosal biopsy?	☐	☐

Interviewer: Provide examples of medicines, if needed.

If no to any, participant is ineligible.

11. In the last 4 weeks, have you used any of the following:

	yes	no
11a. systemic immunomodulatory medications?	☐	☐
11b. rectally administered medications?	☐	☐
11c. rectally administered products (including condoms) that contain N-9?	☐	☐
11d. any investigational products?	☐	☐
11e. post-exposure prophylaxis for HIV exposure?	☐	☐

Interviewer: Provide examples of medicines and/or products, if needed.

If yes to any, schedule the Enrollment Visit at least 4 weeks after last use.

12. Would you be willing to abstain from use of the following during the period of study participation:

	yes	no
12a. systemic immunomodulatory medications?	☐	☐
12b. rectally administered medications?	☐	☐
12c. rectally administered products (including condoms) that contain N-9?	☐	☐
12d. Any investigational products?	☐	☐

Interviewer: Provide examples of medicines and/or products, if needed.

If no to any, participant is ineligible.

Screening Visit Eligibility (non-DataFax) - Page 2

Item-specific Instructions:

- **Items 10a–10f:** If the participant is unfamiliar with any medications listed, provide specific examples. For example, if a participant does not know what a non-steroidal anti-inflammatory drug (NSAID) is the interviewer could say, “for example, ibuprofen (such as Advil or Motrin) or naproxen (such as Aleve).” Any example of a NSAID is fine to mention.
- **Item 10g:** Please provide examples of medicines for this item.
- **Items 11a–11e:** Please provide examples of medicines for these items.
- **Items 12a–12d:** Please provide examples of medicines for these items.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN007 (172)

Participant ID

☐☐☐ – ☐☐☐☐☐ – ☐

Site Number Participant Number Chk

Screening Visit Eligibility

For female participants only.

	yes	no	
13. Are you postmenopausal, meaning have you gone through menopause?	☐	☐	***If yes, go to item 15.***
14. Are you using, or willing to use, an acceptable form of contraception for the duration of the study (acceptable forms of contraception include: barrier methods, IUD, hormonal contraception, surgical sterilization, or vasectomization of male partner)? ***Note: if the female participant has female partners only, this is an acceptable form of contraception (i.e., a barrier method).***	☐	☐	***If no, participant is ineligible.***
15. Are you currently breastfeeding?	☐	☐	
16. Do you intend to breastfeed during study participation?	☐	☐	***If yes to either, participant is ineligible.***

Complete items 17 and 18 after the interview.

	yes	no	
17. Was the subject willing and able to provide adequate locator information, as defined in the site SOP?	☐	☐	***If no, participant is ineligible.***

For female participants of childbearing potential only.

	negative	positive	
18. Screening hCG pregnancy test result:	☐	☐	***If positive, participant is ineligible.***

Screening Visit Eligibility (non-DataFax) - Page 3

Item-specific Instructions:

- **Items 13–16:** These items are for female participants only. For male participants, leave these items blank.

Section 14 – Data Communiqués

For MTN-007, 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-007 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-007 Data Communiqué #1

September 3, 2010

This is official study documentation for MTN 007. Please circulate it among relevant staff for their review, print it, and place it in your MTN 007 Study Specific Procedures (SSP) Manual in the Data Communiqués section. This document is considered part of the MTN 007 SSP manual.

UPDATES

1. Revised Case Report forms – Adverse Experience Log, Pregnancy Outcome, and Medical Eligibility

Since the time MTN-007 CRFs were first distributed (January 2010), protocol changes present in protocol version 2.0 required that three CRFs be revised. A description of the form revisions is provided below.

a. **Adverse Experience Log (AE-1):** Item 4 ("Relationship to Study Product") had its response options changed from 5 categories to 2 ("Related", "Not Related"), along with a revised note below the "Not Related" response category. These changes were made based on the most recent version of the DAIDS EAE Manual. Item 3 ("Severity") had the word "Potentially" added to the description of the "Grade 4" response option. Updates were also made to the form instructions for item 4 based on the revised categories.

b. **Pregnancy Outcome (PO-1, PO-2):** For item 4c-4f, the skip instruction present on the front of the form has been removed. The form instructions for these items has been revised to indicate that the site should refer to the protocol and the DAIDS EAE Manual to determine if the outcome and/or any complications resulting from the pregnancy outcome meet AE or EAE reporting requirements. On page 2, a skip instruction has been added above item 7, indicating that items 7-10 of the form are completed only for live births. A form instruction has also been added for these items with this same instruction.

c. **Medical Eligibility (non-DataFax):** Item 1 of this form has been revised to match the wording of exclusion criterion #2 in the protocol (section 5.3). This item now reads "At screening, did the participant report symptoms and/or have a clinical or laboratory diagnosis of any of the following active rectal or reproductive tract infections".

Once sites receive the revised CRFs, they should use the new CRF versions (dated 18-AUG-10) to replace the previous versions (dated 04-SEP-09). The 04-SEP-09 versions of the above CRFs should be destroyed. For the Medical Eligibility form, you will need to obtain the Screening Visit form packets previously provided and use the new version of this form to replace the old version.

CLARIFICATIONS

1. Anoscopy and Sigmoidoscopy Results CRF, "Bleeding" items (2a, 3a, 5a)

Note that expected spotting/bleeding associated with rectal specimen collection (i.e. biopsy collection) is not considered an abnormal finding. If such spotting/bleeding is observed, document the spotting/bleeding in a chart note, indicating its association with specimen

collection, but not on the Anoscopy and Sigmoidoscopy CRF (do not mark “Bleeding” for items 2a, 3a, or 5a).

2. Documenting reason for unreturned applicators on the Study Product Returns CRF

If a participant does not return all of the expected used and unused product applicators, record in the “Comments” field of the Study Product Returns CRF the reason the applicators were not returned.

3. Interim Visit form instructions, Item 3 (pregnancy testing)

The form instructions on the back of the Interim Visit CRF state that pregnancy testing is done at interim visits only if clinically indicated. However, per protocol, pregnancy testing is *required* at all interim visits for females of childbearing potential. Please disregard the “only if clinically indicated” portion of the instructions for this item (first sentence).

REMINDERS

None.

MTN-007 Data Communiqué #2

September 13, 2010

This is official study documentation for MTN 007. Please circulate it among relevant staff for their review, print it, and place it in your MTN 007 Study Specific Procedures (SSP) Manual in the Data Communiqués section. This document is considered part of the MTN 007 SSP manual.

UPDATES

1. Revised Case Report forms – Medical Eligibility, Screening Visit Eligibility

To better match the eligibility criteria listed in protocol version 2.0, some modifications have been made to these two non-DataFax forms as described below.

a. **Medical Eligibility (non-DataFax):** Item 2e of this form, which asks about excessive daily alcohol use by the participant, has been removed and placed on the (new) Enrollment Visit Eligibility form (non-DataFax). The revised form version has a date of 08-SEP-10.

b. **Screening Visit Eligibility (non-DataFax), pages 1 and 2:** The wording of item 7 (page 1) has been revised to match the corresponding eligibility criterion in the protocol. For this same reason, item 11e (page 2) has been added. Both of these form pages are dated 08-SEP-10 (note that page 3 of this form has mainlined its original date of 04-SEP-09).

2. New Case Report form – Enrollment Visit Eligibility form (non-DataFax)

A new form, Enrollment Visit Eligibility (non-DataFax), has been created and added to the Enrollment Visit packet. This form is completed at the Enrollment Visit, and documents the participant's eligibility for the study based on two eligibility criteria required (per protocol) to be assessed at enrollment. This is a one-page form, dated 08-SEP-10.

SCHARP will send hard-copies of these revised and new CRFs to each site. Once sites receive the revised CRFs, they should use the CRF versions dated 08-SEP-10 to replace the Medical Eligibility and Screening Visit Eligibility forms currently present in their Screening Visit form packets. The old versions of these CRFs should be destroyed.

The new Enrollment Visit Eligibility form needs to be added to all existing Enrollment form packets along with the revised Enrollment Visit Packet cover sheet page (both dated 08-SEP-10). The old version of the Enrollment Visit Packet cover page should be destroyed.

3. Updated Data Collection section of SSP Manual

In order to include the revised and new CRFs described above, the Data Collection section of the MTN-007 SSP Manual will be updated. This revised section (Section 13) will be posted to the MTN-007 webpage shortly, version number of 2.1.

CLARIFICATIONS

None

REMINDERS

None.

MTN-007 Data Communiqué #3

September 23, 2010

This is official study documentation for MTN 007. Please circulate it among relevant staff for their review, print it, and place it in your MTN 007 Study Specific Procedures (SSP) Manual in the Data Communiqués section. This document is considered part of the MTN 007 SSP manual.

UPDATES

1. Revised Enrollment Visit Eligibility case report form (non-DataFax)

The Enrollment Visit Eligibility non-DataFax form has been revised to correct two minor wording errors present on the front of the form. The date of the new form is 22-SEP-10 (bottom left-hand corner). The revised form will be provided to sites as a pdf file, which should be printed (2-sided printing). Please use the revised form dated 22-SEP-10 to replace the current version of this form present in all of the Enrollment Visit form packets present at your site (and remove and destroy the previous version).

CLARIFICATIONS

None

REMINDERS

None.

Not a DataFax form. Do not fax to DataFax.

MTN007 (172)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number Participant Number Chk

Enrollment Visit Eligibility

Form Completion Date

[ ][ ] [ ][ ][ ] [ ][ ]

dd *MMM* *yy*

I now need to ask you one more question regarding your study participation. There is no right or wrong answer, so please be as honest and as accurate as you can.

1. Do you agree to not participate in any other trials involving drugs, medical devices, or genital products while you are on this study? .....

yes	*no*
☐	☐

If no, participant is ineligible.

End of interview.

2. *Within the past 12 months, did the participant report a history of excessive daily alcohol use (as defined by the CDC as heavy drinking consisting of an average consumption of more than 2 drinks per day for men, and more than 1 drink per day for women), frequent binge drinking, or illicit drug use that includes any injection drugs, methamphetamines (crystal meth), heroin, or cocaine, including crack cocaine? .....*

yes	*no*
☐	☐

If yes, participant is ineligible.

Enrollment Visit Eligibility (non-DataFax) - Page 1

Purpose: This form is used at the Enrollment Visit to document the participant's eligibility with regard to two eligibility criteria. This form is completed once, at the participant's Enrollment Visit.

General Information/Instructions: This is a mixed form—one item (item 1) is interviewer administered while item 2 is not. 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 Enrollment Visit Eligibility form must be completed as part of the subsequent screening attempt. See the Data Collection Section of the Study-Specific Procedures (SSP) Manual for more instructions regarding re-screening form completion procedures.*

MTN-007 Data Communiqué #4

November 10, 2010

This is official study documentation for MTN 007. Please circulate it among relevant staff for their review, print it, and place it in your MTN 007 Study Specific Procedures (SSP) Manual in the Data Communiqués section. This document is considered part of the MTN 007 SSP manual.

UPDATES

1. Revised LDMS Specimen Tracking Sheet – Version 2.0, dated 01-NOV-10

The LDMS Specimen Tracking Sheet (non-DataFax) has been revised to reflect changes to the processing instructions for the ARB and FSR biopsy specimens for cytokines. The revised version (v2.0) was distributed to sites via email on November 1, 2010. Sites are required to print the 2-page form and use it to replace current versions of the form present on-site. This includes bulk supplies of this form as well as LDMS forms present in the Enrollment, Treatment 1, and Final Clinic Visit CRF packets.

2. Timing of Pre-existing Conditions form completion

Per protocol version 2.0, the Pre-existing Conditions assessment and form completion first occurs at the Screening Visit. Note that the Pre-existing Conditions form is included in the Enrollment Visit CRF packet. As such, please remove the Pre-existing Conditions form present in all unused Enrollment Visit packets and move it to the Screening Visit packet. The visit checklists will correctly prompt you to complete this form at the Screening Visit, and update it at the Enrollment Visit.

CLARIFICATIONS

1. Biopsy collection sites – normal or abnormal finding?

Note that biopsy collection sites that are healing normally and as expected are considered normal findings. Normally-healing biopsy sites should be documented as “normal findings” on the Anoscopy and Sigmoidoscopy Results form (items 2, 3, and 5),

2. Completion of Severity Grade, AE Log Page #, and Not Reportable as an AE fields of the Laboratory Results form (LR-1, LR-2)

For non-gradable (Grade 0) lab values, leave the “Severity Grade”, “AE Log Page #”, and “Not reported as an AE” boxes of the LR form blank. If a lab value is grade 1 or higher, record the severity grade and complete either the “AE Log Page #” field or the “Not reported as an AE” field as applicable.

REMINDERS

None.

MTN-007 Data Communiqué #5

February 18, 2011

This is official study documentation for MTN-007. Please circulate it among relevant staff for their review, print it, and place it in your MTN-007 Study Specific Procedures (SSP) Manual in the Data Communiqués section. This document is considered part of the MTN-007 SSP manual.

UPDATES

None.

CLARIFICATIONS

1. Classification of normally-healing biopsy collection sites as normal findings

Note that biopsy collection sites that are healing normally and as expected are classified as "normal findings" on the Anoscopy and Sigmoidoscopy Results form (ASR-1 items 2, 3, and 5),

2. STI Laboratory Results - Item 1a

This item (1a) is where the site records the result of the HIV EIA test performed by study staff. The instructions for this item specify a non-rapid HIV EIA in error – this item is used to document both rapid and non-rapid HIV EIA test results as performed by study staff.

REMINDERS

None.

Section 15 - Study Reporting Plan

MTN-007 Statistical and Data Management Center (SDMC) Staff

Protocol Statistician:	James Dai
Project Manager:	Missy Cianciola
Statistical Research Associates:	Marla Husnik, Jason Pan
Protocol Programmer:	Katie Weaver
Data Coordinator:	Sue Tracy-Waisanen
Technical Document Specialist:	Stacie Kentop
Laboratory Programmer:	Laura Robins-Morris
Clinical Affairs Safety Associate	Yevgeny Grigoriev
CASI Programmer	Lynda McVarish

15.1 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-007.

This reporting plan will:

- Identify the purpose and content of each report;
- Identify those responsible for the preparation and distribution of each report;
- Identify who should review the reports so that corrective action (if necessary) is taken; and
- Ensure the Protocol Team approves the plan prior to study initiation.

This reporting plan was prepared by the MTN 007 SDMC Project Manager in collaboration with other MTN-007 SDMC staff.

15.2 Study Reports

Table 15-1 lists the reports the SDMC will produce and distribute via email. Table15-2 lists the reports the SDMC will produce and make available via the Atlas website:

http://atlas.scharp.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 15-1: MTN-007 SDMC Reports Distributed via Email

Report Title	Distribution Frequency	Email Distribution List
Data Quality Control (QC)	Every two weeks, or as needed	• Site Study Coordinators • Site Data Managers • CORE Clinical Research Managers • SDMC Project Manager
Clinical Data Quality Control (CQC) Queries	Monthly, or as needed	• Site Study Coordinators • Site Data Managers • CORE Clinical Research Managers • SDMC Project Manager
Unresolved Adverse Experiences Listing	Monthly, or as needed	• Site Study Coordinators • Site Data Managers • CORE Clinical Research Managers • SDMC Project Managers
Site-specific Specimen Monitoring Report	Monthly	• Site Study Coordinators • Network Lab Representative • SDMC Project Manager
Summary Specimen Monitoring Report	Monthly	• Network Lab Representative • SDMC Project Manager

Table 15-2: MTN-007 SDMC Reports Posted on Atlas

Report Title	Update Frequency	Atlas Viewing Area
Enrollment and Retention	Daily	Unsecure
Visit Adherence and Procedure Completion	Monthly	Unsecure
Site Data Management Quality	Monthly	Unsecure
Safety (PSRT) Report	One week prior to each scheduled PSRT call	Secure
Study Monitoring Committee (SMC)	As determined by the SMC	Secure
Network Lab Assay Results Report	Weekly, starting once results are received from the Network Lab	Unsecure

15.2.1 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.

15.2.2 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.

15.2.3 Unresolved Adverse Experiences Listing

Purpose: To identify those AEs that have been marked as "Continuing" for >90 days, to help individual sites monitor AE resolution throughout the study.
Prepared and Distributed by**:** SDMC Reports Programmer and SDMC Clinical Affairs Safety Associate
Components: Site-specific listing of all AEs that have been marked as "Continuing" for >90 days. For each unresolved AE the report lists the PTID, page #, AE text, date reported to site, onset date, severity grade, and visit at which the AE was first reported.

15.2.4 Site-Specific 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.

15.2.5 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.

15.2.6 Enrollment and Retention Report

Purpose: To monitor participant accrual and retention as reflected by data submitted to SCHARP DataFax
Prepared by: SDMC Protocol Programmer

Components: *Enrollment*: this report includes the number of men and women enrolled each week and cumulatively. *Retention, by visit*: this report includes the total number of men and women 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.

15.2.7 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 days/ranges and actual visit dates, and the number of days between sequential follow-up visits. Listing of number and % of required blood specimens collected, rectal specimens collected, lab tests completed, pregnancy tests completed, and HIV tests completed.

15.2.8 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. Report includes a table with data from the previous month and a table with cumulative data since study start.

15.2.9 Safety (PSRT) Report

Purpose: To help the Protocol Safety Review Team monitor study participant safety as reflected by adverse experiences reported to the SDMC via SCHARP DataFax
Prepared by: SDMC Reports Programmer and SDMC Clinical Affairs Safety Associate
Components: Cumulative AE data as well as product holds/discontinuations reported to SCHARP via DataFax. Report may include other DataFax data as requested by the PSRT.

15.2.10 Study Monitoring Committee Report

Purpose: To monitor study progress at each site as outlined by the protocol
Prepared and Distributed by: Prepared by SDMC MTN 007 staff and distributed by SDMC Project Manager
Components: Summary (by site and for the study overall) of study design and history, accrual, retention, demographics, and visit adherence. Site data

management quality, and other components as requested by the SMC.

15.2.11 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 Specimen Storage CRF data) along with the number and percentage of results received and processed at SCHARP.

Section 16. Behavioral Measures: Web-based Questionnaires and Phone Reporting System

There will be three sets of behavioral measures collected in MTN-007: the Baseline Behavioral Questionnaire, the Adherence Questionnaire, and the Product Acceptability Questionnaire. The Baseline Behavioral Questionnaire will be used to collect information on all participants' sexual behaviors, use of rectal products, drug and alcohol use, and knowledge of microbicides, amongst other things. The Product Acceptability Questionnaire will be administered to participants in the gel arms only and will be used to collect information on participants' experiences with the gel and their anticipated likelihood to use a rectal microbicide in the future. Data collection for the Baseline Behavioral and Product Acceptability questionnaires will be done by means of Web-based technology that is a variation of Computer Assisted Self-Interview (CASI), with the only difference being that the data entered are not stored in a laptop or PC but rather transmitted instantly to a server selected by SCHARP. The questionnaires are not accessible to people who are not participating in the study.

The Adherence Questionnaire will be administered to participants in the gel arms only and will be used to collect information about participants' use of study product starting at the Treatment 2 Visit. The Adherence Questionnaire is administered via the Phone Reporting System (PRS). Participants randomized to the gel arms will be asked to call in daily each time they use the gel at home and answer a series of questions on their use of study product. The information collected will be used to measure the participant's adherence to product.

The timing of these questionnaires is listed below.

Table 1: Timing of Behavioral Measures

Study Visit	Behavioral Measures
Enrollment Visit	Baseline Behavioral Questionnaire (CASI)
Treatment 2 Visit	Adherence Questionnaire (Phone Reporting System)
Final Clinic Visit	Product Acceptability Questionnaire (CASI)

The purpose of this SSP section is to help sites 1) get the equipment ready for the participant to respond to the Web-based questionnaires and 2) explain to the participant how to use the PRS.

16.1 GENERAL COMPUTER USE

Each study site will have a PC or laptop connected to the Web for the participants to use. Sites should select a location in the research offices for the PC or laptop that is private (i.e. the screen should be out of sight to 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. As such, staff members should be familiar with the questionnaire in case participants raise any questions. There should be an electrical outlet and a jack for broadband connection, unless a reliable wireless connection is used. The PC or laptop should be plugged into an AC power source. An external mouse should be connected to the laptop. To minimize problems with computers, keep the laptop plugged into a power source, avoid having food or drink nearby, and keep the area where the computer is used clutter-free. You should have a virus program installed on your computer. It is recommended that each site have a back-

up laptop or desktop available for use, in the event that the designated computer does not work. Refer to the operations manual of the PC or laptop for hardware and software specifications, and instructions on how to use the computer (i.e., turning a computer on and off). Each site is responsible for addressing issues of security, privacy, background noise, lighting, ergonomics, and overall participant comfort in its site-specific study operating procedures.

Please refer to Section 16.3 for guidelines and contact information regarding troubleshooting and problems with administering the questionnaires.

For questions regarding general computer problems, please refer to Section 16.3 in this manual for contact information.

16.1.1 Using a Mouse with a Laptop Computer

Sites have the option of using a desktop computer or a laptop. If a laptop is used, the following instructions on the use of a mouse with a laptop are provided. 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. Sites may use either a regular mouse connected through the laptop's USB port, or a cordless mouse.

To connect a cordless mouse:

- 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 the 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 or down, 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 cordless mouse for convenient storage. This turns the mouse off. To turn the 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.

16.2 ADMINISTERING BEHAVIORAL MEASURES

As mentioned in Table 1, the Behavioral Measures will be collected three times during the course of the study:

- Enrollment Visit: Baseline Behavioral Questionnaire
- Treatment 2 Visit: Adherence Questionnaire assessed with the PRS
- Final Clinic Visit: Product Acceptability Questionnaire

If a participant in any of the gel arms discontinues trial participation early, he/she will be encouraged to respond to the Product Acceptability Questionnaire at the time he/she exits the study (early termination visit).

16.2.1 Administering the Baseline Behavioral Questionnaire (Enrollment Visit)

To begin, access the Web page for the Baseline Behavioral Questionnaire using Internet Explorer at the following URL:

http://www.scharp.org/MTN007baseline

Note. If you use browsers other than Internet Explorer, the questions and response choices may not display correctly.

Once the questionnaire is accessed, staff should complete the following:

1) Log in by entering the PTID (without spaces or hyphens), Study Code (MTN007). and re-entering the PTID (without spaces or hyphens) for confirmation.
2) Enter the visit code. The acceptable range for the Baseline Behavioral Questionnaire is 2.0 to 2.9.
3) Enter the current date by selecting the month, day and year from the drop down menus.
4) 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).
5) Verify the participant's comfort with using the mouse and keyboard, and navigating through the questionnaire.
6) Initially, the participant will be presented with simple practice questions (e.g. "choose all that apply", "indicate how many times", "choose one of a fixed set of answers", etc.) Allow the participant to complete the practice questions, assisting him/her if needed, to make sure he/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 (i.e., numbers that are out of the possible range, e.g. saying he/she used the gel 100 times).
7) Let the participant know that he/she can refuse to answer any question.

Note: If the participant is unsure of his/her answer, encourage the participant to make his/her best guess rather than refuse. Answer any questions that the participant may have and let the him/her know that you are available for help.

8) Instruct the participant to get you once he/she sees a message at the end of the questionnaire indicating that he/she has completed the questionnaire which states: PLEASE STOP HERE AND TELL INTERVIEWER THAT YOU ARE FINISHED, or if he/she needs/wants to stop the questionnaire before reaching the end.

9) Leave the room and allow the participant to proceed to the Baseline Behavioral Questionnaire and respond to the questionnaire on his/her own. The participant should be the only person in the room at the time he/she is completing the questionnaire.

10) When the participant calls you, enter the password: 2010.

11) Use the comments field on the following screen to enter information about any deviations from the behavioral measures protocol or any problems with the web-based questionnaire.

Please refer to Section 16.3 below for guidelines and contact information regarding troubleshooting and problems with administering the questionnaire.

16.2.2 Administering the Adherence Questionnaire using the PRS (Treatment 2 Visit)

At the Treatment 2 visit, the study coordinator will instruct the participant on using the PRS to report gel use during the 7 days he/she is using the product. The PRS call to train participants on use of the system will be placed using a mock PRS ID and PIN (a range of PTIDs have been assigned for each study site).

Instructions for using PRS:

1) Provide the participant with his/her five-digit PRS ID, PIN, and the toll free access number for the PRS (1-866-365-7233). This is for their information and not for the call that will be placed for training purposes (see instructions below).

   Note: PRS ID number consists of the first 3 digits and the 7th and 8th digit of the PTID (e.g., if PTID is 999-00101-5, the PRS ID is 99901). The PIN that is unique to each PRS ID can be found in the list distributed to the sites.

2) Instruct the participant to program the toll free number in his/her cell phone, if he/she has one and is comfortable with doing that. Inform the participant that he/she can access the PRS from any telephone.

3) Inform the participant that he/she should call the PRS call the system immediately after applying the product during the seven days that he/she is using the study product.

4) Inform the participant that he/she will receive $2 per phone call (maximum $14) and has until midnight of each day to call. If the participant calls every day during the seven days he/she is using the product, he/she will also receive a bonus of $10. Inform the participant that if he/she forgets to call for one or more days, he/she will still receive the full amount accumulated per call, but will not get the additional $10 bonus. In addition, let the participant know that you will contact him/her if he/she has

not called the PRS for 48 consecutive hours, in order to make sure that he/she is not having problems with the PRS.

5) Explain to him/her that the PRS is a pre-recorded system that will ask him/her questions on product use and sexual behavior. Describe the questions the participant will hear when he/she calls the PRS. Instruct the participant to be as honest as possible when answering the questions in the PRS. His/her responses will help us to develop a product that will be useful to people like him/her.
6) Alert the participant that the PRS should not be used for reporting to the clinic staff any medical problems that may result from gel use. If the participant has any medical problems such as burning, irritation, diarrhea, etc., he/she should contact the clinic staff.

Training Call Instructions:

1) Set the phone to speakerphone so that you can guide the participant during the first call to the PRS.
2) Instruct the participant to access the PRS by dialing the toll free number 1-866-365-7233, and to use the touchpad to enter his/her answers.
3) Enter the mock PRS ID and then its corresponding PIN.
4) Let the participant know that he/she would enter his/her own PRS ID and PIN.
5) Allow the participant to proceed with the PRS and to respond on his/her own.
6) Answer any questions the participant may have about how to use the PRS.

Using the PRS:

After entering the PRS ID and PIN number, the participant will respond to pre-recorded questions on product use. Responses can be entered by either pressing keys (1 for yes, 2 for no) or by voice response that is understood and registered by the system. Participants receive a small monetary incentive for each call regardless of their report of product use or lack of use; furthermore, a bonus at the end of the seven days is accrued by those who have not missed any day in calling the system.

When a participant has not called the system in 48 hours, an alert is automatically generated and sent by email to a staff member of the behavioral team at Columbia University and the study coordinator at the study site. The study coordinator should then contact the participant to inquire about missed calls (if the participant forgot to call) and adherence to the study product regimen, and to remind participants to call the PRS immediately after applying the product. A log will be kept by the behavioral team about any missed calls beyond 48 hours noting the reminder call placed by the study coordinator and its outcome.

Given that participants are instructed to use the product at bedtime and to call the system immediately after applying the product, the calls are a proxy for compliance with time of application; in addition, participants will be reporting whether they used the product, which will constitute one measure of study product adherence. Since participants will be asked to return in separate, sealed bags both used and unused applicators, we will be able to cross-validate self-reports and applicator counts to assess adherence.

16.2.3 Determining Compensation Owed for PRS (prior to Final Clinic Visit)

Study coordinators will provide compensation to each participant for having called the PRS at his/her Final Clinic Visit. In order to determine the compensation owed, the following procedures will be followed:

1) Study coordinators will email Rebecca Giguere at giguere@pi.cpmc.columbia.edu to alert her of the date and time of each participant's scheduled Final Clinic Visit.

2) The day before the participant's Final Clinic Visit, Rebecca will email the study coordinator to inform him/her of the approximate compensation owed to the participant for having called the PRS.

For example: Participant 999-00146-3 has called the PRS six times. So far, the participant has accumulated $12. If the participant makes the final call tonight, the total compensation owed will be $24. ($2 per call plus a $10 bonus for calling every day).

Or

For example: Participant 999-00146-3 has called the phone diary five times. So far, the participant has accumulated $10. The participant missed a call on Monday, November 15th, 2010, so we cannot give him/her the $10 bonus. If the participant calls tonight, the total compensation owed will be $12.

3) The day of the Final Clinic Visit, Rebecca will email the study coordinators to confirm the final amount of compensation owed.

For a Final Clinic Visit scheduled in the early morning:

Rebecca will make every effort to provide a confirmation to the study coordinators of the total amount of compensation owed to each participant. However, if a participant's Final Clinic Visit is scheduled early in the morning, Rebecca may not have had the chance to review the data prior to the visit. Therefore, if study coordinators have not received an email from Rebecca with the confirmation at the time of the Final Clinic Visit, they should ask participants if they called the PRS the night before, and provide them with compensation accordingly.

16.2.4 Administering the Product Acceptability Questionnaire (Final Clinic Visit)

To begin, access the Web page for the Product Acceptability Questionnaire at the following URL:

http://www.scharp.org/MTN007accept

Note. If you use other browsers other than Internet Explorer, the questions and response choices may not display correctly.

1) Log in by entering the PTID (without spaces or hyphens) and Study Code (MTN007) and re-entering the PTID (without spaces or hyphens) for confirmation.

2) Enter the visit code. The acceptable range for the Product Acceptability Questionnaire is 3.0 to 6.9.

3) Enter the current date by selecting the month, day and year from the drop down menus.

4) 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).

5) Verify the participant's comfort with using the mouse and keyboard, and navigating through the questionnaire.

6) Initially, the participant will be presented with simple practice questions (e.g. "choose all that apply", "indicate how many times", "choose one of a fixed set of answers", etc.) Allow the participant to complete the practice questions, assisting him/her if needed, to make sure he/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 (i.e., numbers that are out of the possible range, e.g. saying he/she used the gel 100 times).

7) Let the participant know that he/she can refuse to answer any question.

   Note: If the participant is unsure of his/her answer, encourage the participant to make his/her best guess rather than refuse. Answer any questions that the participant may have and let the him/her know that you are available for help.

8) Instruct the participant to get you once he/she sees a message at the end of the questionnaire indicating that he/she has completed the questionnaire which states: PLEASE STOP HERE AND TELL THE INTERVIEWER THAT YOU ARE FINISHED, or if he/she needs/wants to stop the questionnaire before reaching the end.

9) Leave the room and allow the participant to proceed to the Product Acceptability Questionnaire and respond to the questionnaire on his/her own. The participant should be the only person in the room at the time he/she is completing the questionnaire.

10) When the participant calls you, enter the password: 2010.

11) Use the comments field on the following screen to enter information about any deviations from the behavioral measures protocol or any problems with the web-based questionnaire.

Please refer to Section 16.3 below for guidelines and contact information regarding troubleshooting and problems with administering the questionnaire.

16.3 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 ***mtn007webtrouble@mtnstopshiv.org***. The team of staff members (Missy Cianciola and Lynda McVarish at SCHARP; and Curtis Dolezal and Rebecca Giguere at the HIV Center) will be available to assist you to troubleshoot and resolve any problems you may have with the Web-based questionnaires.

To facilitate the troubleshooting process, please indicate in your email a description of the problem, including a copy of the error message(s), if any, and date and time of when the problem occurred. It is very useful to the MTN 007 Web Trouble 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 by clicking on the middle box containing one square located at the top right corner of the screen, and then 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 into the Word document (click on Edit and then Paste; or simply hit CTRL and V simultaneously). Save the Word file as MTN007WebProblem[insert date].doc and attach it to your email to the MTN 007 Web Trouble team. An example of an email message to the Web Trouble team is presented on the next page.

16.4 Participants Who Discontinue Study Product

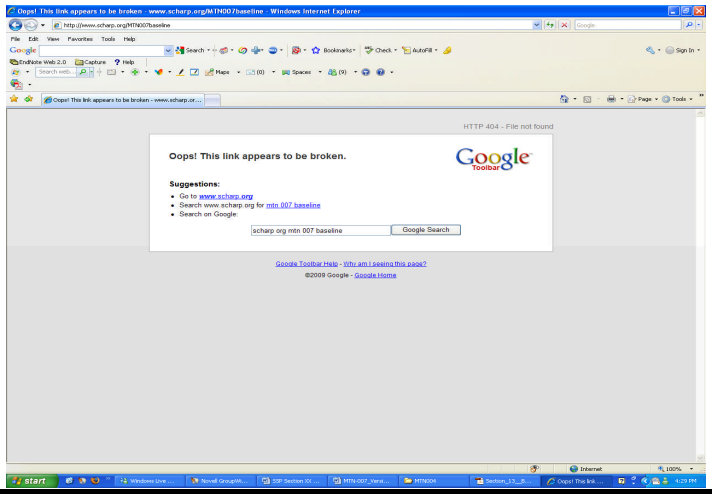
As outlined in Section 6.8: Modified Follow-up Procedures, participants who permanently discontinue study product will not be routinely withdrawn from the study and every effort should be made to complete all protocol-specified visits and procedures, including the behavioral measures. Therefore, even if a participant discontinues study product, he/she should continue to call the Phone Reporting System and should complete the Product Acceptability Questionnaire at the Final Clinic Visit.

Email Message

To: **mtn007webtrouble@mtnstopshiv.org**
From: XXX
Date: July 30, 2009, 10:28am EST
Re: MTN 007 Web Problem

No access to the Baseline Behavioral Questionnaire (www.scharp.org/MTN007baseline) on July 30, 2009 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 generated using Ctrl + Print Screen should be attached to the email (example of filename: MTN007WebProblem_7-30-09.doc)]



The following mock PTIDs and/or PRS IDs will be used to troubleshoot any problems:

MOCK Participant ID's:

PTID	PRS ID	PIN
999-00146-3	99946	8571
999-00147-4	99947	1598
999-00148-9	99948	9341
999-00149-7	99949	4349
999-00150-0	99950	6398

Rebecca Giguere will coordinate efforts to quickly resolve any problems. She will keep a record of any problems in a log (MTN 007 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:

- Rebecca Giguere at (212) 543-5829 or giguere@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 link to the Web page again to log the participant in. The system should return to where the participant left off (i.e., the Web page with the question where a participant left off should be displayed). If the problem persists, contact mtn007webtrouble@mtnstopshiv.org and call Rebecca Giguere so that actions can be taken immediately. The MTN 007 Web Trouble 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 007 Web Trouble Log.

Refer to Appendix 16-1 for "Quick Tips for Web-Based Behavioral Measures"
Refer to Appendix 16-2 for "Quick Tips for Phone Reporting System"
Refer to Appendix 16-3 for the Behavioral Measures

Section Appendix 16-1

QUICK TIPS FOR WEB-BASED QUESTIONNAIRES

- Prior to starting a questionnaire, make sure that the external mouse is connected and working properly.

- Make sure that the participant is comfortable and has privacy to assure the confidentiality of his/her responses.

- Start the questionnaire by typing the Web address to the corresponding Behavioral Measure, using Internet Explorer:

    1. Baseline Behavioral Questionnaire (Enrollment Visit)
    http://www.scharp.org/MTN007baseline

    2. Product Acceptability Questionnaire (Final Clinic Visit)
    http://www.scharp.org/MTN007accept

- Make sure that the participant is comfortable with using the mouse and keyboard.

- Check to confirm that it is the correct questionnaire.

- Enter PTID, Study Code: MTN007, and enter PTID again to confirm.

- Enter the visit code.

- Enter the current date.

- Allow participant to complete the practice questions.

- Assist the participant as needed.

- Instruct the participant that when he/she reaches the end of the survey, he/she will see a screen that says “PLEASE STOP HERE AND TELL THE INTERVIEWER THAT YOU ARE FINISHED." The participant is not finished until he/she reaches this end screen. At that point the participant should leave the computer as is and inform the study coordinator.

- Enter the password: 2010. Enter comments on the following screen if there were any problems with the web-based questionnaires or protocol deviations. 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, restart the questionnaire by going to the appropriate link for the Web page and logging in with the PTID and study code.

- If you encounter any problems with the questionnaires or with the laptop/desktop that you are using, notify mtn007webtrouble@mtnstopshiv.org.

Section Appendix 16-2

QUICK TIPS FOR THE PHONE REPORTING SYSTEM

- Prior to calling the PRS, make sure that the telephone is working properly.
- Provide the participant with his/her PRS ID, PIN, and the toll free access number for the PRS (1-866-365-7233).
- Set the phone to speakerphone so that you can guide the participant during the training call to the PRS.
- Dial the toll free number 1-866-365-7233 and enter a mock PRS ID and PIN using the touchpad.
- Allow the participant to proceed with the PRS and to respond on his/her own.
- Assist the participant as needed.
- If you encounter any problems with the PRS, notify Rebecca Giguere at (212) 543-5829 or giguere@pi.cpmc.columbia.edu.

Section Appendix 16-3 Behavioral Measures

Section I: Baseline Behavioral Questionnaire

Table of Contents

TEXT IN CAPITAL LETTERS SHOULD NOT BE PRESENTED TO THE PARTICIPANT.

THE SYSTEM GENERATES AN “X-VALUE” VARIABLE FOR ALL NUMERIC VARIABLES (RESPONSES ARE IDENTICAL TO THE ORIGINAL RESPONSES BUT ALSO INCLUDE VALUES FOR THE REFUSE-TO-ANSWER OPTION). FOR DATA ANALYSIS, WE WILL USE THE ORIGINAL VARIABLE, NOT THE SYSTEM GENERATED X-VALUE VARIABLE.

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. [*Question 1*]

Click the "NEXT" button to go to the next screen.

Introduction *[Question 2]*
Good! You can always move to the next screen by clicking "next", or, to go to the previous screen, click on the browser's "back" arrow at the top of the screen.
Click the "NEXT" button to go to the next screen.

****

Practice *[Question 3]*

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]
3.1 Eggs
3.2 Cheese
3.3 Croutons
3.4 Salad Dressing
3.5 Carrots
3.6 Bacon bits
3.7 None of the above

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 4]*

Do you like summer?
Yes
No
Refuse to answer

This is an example of a single response question:
If you want to change your response, simply click the response you want.

****

****

Practice *[Question 5]*

This question shows how to use your mouse to scroll over a word to see its meaning or alternate phrases. Use the mouse to put the arrow or cursor on the word in bold in the following sentence:

[SCREEN TIPS WILL BE GENERATED FOR WORDS IN BOLD TO DISPLAY THEIR MEANINGS AND ALTERNATE PHRASES, AS PER THE FOLLOWING:]

How many times have you eaten **dessert [SCREEN TIP: SWEETS, ICE CREAM, CAKE, CHOCOLATE]** in the past five days?

For questions that ask the number of times, if you are unsure just give your best estimate.

****

Practice *[Question 6]*

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:

In general, how much do you like ice cream?

1——2——3——4——5——6——7——8——9——10

Dislike very much — Like very much

11. Refuse to answer

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

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **999** IN THIS SECTION.

1 SYSTEM TO RECORD TODAY'S DATE

_____/_____/_____
mm dd yyyy

2 How old are you? _____ (In years)
___ Refuse to answer

3 Please indicate the highest education level you achieved
1. ☐ eighth grade or lower
2. ☐ partial high school
3. ☐ high school graduate/GED
4. ☐ partial college
5. ☐ college graduate
6. ☐ partial graduate school
7. ☐ graduate school degree
8. ☐ Refuse to answer

4 Do you consider yourself…
_____ 1 Hispanic or Latino/a? [SKIP TO Q 5L]
_____ 2 Not Hispanic or Latino/a?
_____ 3 Refuse to answer

5 Do you consider yourself… [SKIP TO Q 6]
1. ☐ American Indian / Alaska Native
2. ☐ Asian
3. ☐ Native Hawaiian or other Pacific Islander
4. ☐ Black or African American
5. ☐ White
6. ☐ Other (please specify) _____
7. ☐ Refuse to answer

5L As a Hispanic or Latino/a person, do you also consider yourself…
1. ☐ American Indian / Alaska Native
2. ☐ Asian
3. ☐ Native Hawaiian or other Pacific Islander
4. ☐ Black or African American
5. ☐ White
6. ☐ Other (please specify) _____
7. ☐ Refuse to answer

6 Are you…
_____ 1 Male? [SKIP TO Q 7]
_____ 2 Female? [SKIP TO Q 7]
_____ 3 Transgender? (If yes, specify:_____)
_____ 4 Other? (If yes, specify:_____
_____ 5 Refuse to answer

6x. Since you did not select “Male” or “Female” for the previous question, we need to ask you about your physical body. This is information that will allow us to know what questions are appropriate for you as the survey continues.

Which of the following is true?

___ 1. I have a penis
___ 2. I have a vagina

7 Do you consider yourself (check all that apply)…

_____ 1 Gay/lesbian/homosexual?
_____ 2 Bisexual?
_____ 3 Straight/heterosexual?
_____ 4 Other? (specify:_____)
_____ 5 Refuse to answer

8 Please check all that apply to your current occupational status.

_____ 1 Full time work
_____ 2 Part time work
_____ 3 Full or part time in school
_____ 4 Neither work nor in school
_____ 5 On disability
_____ 6 Other (specify:_____)
_____ 7 Refuse to answer

9 During the last 12 months, what was your total personal income from all sources?

_____ 1 $10,000 or less
_____ 2 $10,001 to $20,000
_____ 3 $20,001 to $40,000
_____ 4 $40,001 to $60,000
_____ 5 $60,001 to $80,000
_____ 6 Over $80,000
_____ 7 Don’t know
_____ 8 Refuse to answer

SECTION B.1 SEXUAL BEHAVIOR [MEN- IF ANSWER TO Q A.6 = 1]

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **901** IN THIS SECTION.

The following questions refer to your sexual behavior during the past three months that is, from [CASI: INSERT TODAY'S DATE THREE MONTHS AGO] until today.

Sometimes talking about sex can be confusing because people have so many different words to describe body parts and sexual activities. Before we start, we're going to take a minute to review some words so it is clear what we are asking.

[SCREEN TIPS WILL BE GENERATED FOR WORDS IN BOLD TO DISPLAY THEIR MEANINGS AND ALTERNATE PHRASES, AS PER THE FOLLOWING:]

Penis is the male sex organ. Some people call it "dick" or "cock."

Vagina is the female sex organ. Some people call it "pussy."

Rectum and anus are frequently called "butt" or "asshole."

Anal intercourse is when a man puts his penis in another man's or a woman's rectum or anus; some people call this "butt fucking."

Vaginal intercourse is when a man puts his penis into a woman's vagina; some people call this "fucking" or "screwing" or "having sex."

Oral sex is when people put their mouths or tongues on each other's sex organs. When someone does this to a man's penis, some people call this a "blow job." When someone does this to a woman's vagina, some people call this "going down on her."

As you go through the following questions, these words will sometimes appear in bold. If you are not sure what a word in bold means, use the mouse to place the arrow or cursor on the bolded word to see its meaning.

Since the focus will be exclusively on anal, vaginal or oral sex, do *NOT* include in your answers references to partners with whom you did not engage in anal, vaginal, or oral sex.

SEXUAL BEHAVIOR WITH MEN

First, I will ask you about your sexual behavior with men.

1. During the past three months, how many male sexual partners have you had?

_____ [IF 0, SKIP QUESTIONS ON SEX WITH MEN AND GO TO QUESTIONS ON SEX WITH WOMEN.]

_____ Refuse to answer

1x. You responded Refuse to answer for the previous question. Is it true you are unwilling to answer questions about male partners?

1. _____ Yes, I refuse to answer questions about male sexual partners
2. _____ No, I am willing to answer questions about male sexual partners

Of these, how many do you consider to be ...(Please put a number in each box. Enter 0 (zero) if none. Your answers must add up to _____ [CASI PROGRAMMER: ENTER NUMBER FROM Q1]):

1A.1 lovers (men with whom you've felt emotionally involved in a committed relationship and with whom you had sex - like a spouse equivalent or boyfriend)

_____

1A.2 one-night stands (men with whom you had sex only once)

_____

1A.3 other male partners (men with whom you had sex who are neither your lovers nor one-night stands)

_____

1AX.1 Refuse to answer

Receptive Anal Intercourse

In the past three months.....

2. How many times did a male partner put his **penis** in your **rectum**?

_____ [IF 0, GO TO Q 9.]

_____ Refuse to answer

[CASI PROGRAMMER: IF RESPONSE IS "0", ALSO SKIP QUESTIONS IN SECTION D (LUBRICANT USE), WHICH ARE CONTINGENT ON RAI IN THE PAST 3 MONTHS.]

3. How many times did a male partner put his **penis** in your **rectum** without a condom?

_____ [IF 0, GO TO Q 9.]

_____ Refuse to answer

[CASI PROGRAMMER: IF RESPONSE IS "0", ALSO SKIP QUESTIONS B IN SECTION F (SUBSTANCE USE), WHICH ARE CONTINGENT ON URAI IN THE PAST 3 MONTHS.]

4. How many men put their **penis**es in your **rectum** without a condom?

_____

_____ Refuse to answer

[CASI, IF Q 4 = 1 (i.e., THE PARTICIPANT REPORTS THAT ONLY ONE MAN PENETRATED HIM WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 5; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 6]

You said that one man put his penis in your rectum without a condom.

5. Regarding this man (please select one answer).....
___ 1. This man told you he was HIV negative and you had no reason to doubt it.
___ 2. You knew this man was HIV positive.
___ 3. You were not completely sure of this man's HIV status.
___ 4. Refuse to answer

[CASI, IF Q 4 IS 2 OR MORE (I.E., THE PARTICIPANT REPORTS THAT TWO OR MORE MEN PENETRATED HIM WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 6; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 9]

You said ___ men [CASI CAN INSERT THE NUMBER FROM THE PREVIOUS QUESTION (Q 4)] put their penises in your rectum without a condom.

6.1 (6.) Of those men, how many had actually told you they were HIV-negative and you had no reasons to doubt it?

_____

6.2 (7.) Of those men, how many do you know to be HIV-positive?

_____

6.3 (8.) How many were you NOT completely sure about their HIV status?

_____

6X.1 Refuse to answer

Insertive Anal Intercourse
In the past three months.....

9. How many times did you put your penis in a man's rectum?

_____ [IF 0, GO TO Q 16]

_____ Refuse to answer

10. How many times did you put your penis in a man's rectum without a condom?

_____ [IF 0, GO TO Q 16]

_____ Refuse to answer

11. Into how many men's rectums did you put your penis without a condom?

_____

_____ Refuse to answer

[CASI, IF Q 11 = 1 (I.E., THE PARTICIPANT REPORTS THAT HE PENETRATED ONLY ONE MAN WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 12; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 13]

You said you put your penis in one man's rectum without a condom.

12. Regarding this man (please select one answer).....
___ 1. This man told you he was HIV negative and you had no reason to doubt it.
___ 2. You knew this man was HIV positive.
___ 3. You were not completely sure of this man's HIV status.
___ 4. Refuse to answer

[CASI, IF Q 11 IS 2 OR MORE (I.E., THE PARTICIPANT REPORTS THAT HE PENETRATED TWO OR MORE MEN WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 13; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 16]

You said you put your penis in ___ men's [CASI CAN INSERT THE NUMBER FROM THE PREVIOUS QUESTION (Q 11)] rectums without a condom.

13.1 (13.) Of those men, how many had actually told you they were HIV-negative and you had no reasons to doubt it?

_____

13.2 (14.) Of those men, how many do you know to be HIV-positive?

_____

13.3 (15.) How many were you NOT completely sure about their HIV status?

_____

13X.1 Refuse to answer

Oral Sex

In the past three months.....

16. How many times did you put another man's penis in your mouth?

_____ [IF 0, GO TO Q 19]

_____ Refuse to answer

17. How many times did you put another man's penis in your mouth without a condom?

_____ [IF 0, GO TO Q 19]

_____ Refuse to answer

18. How many men's penises did you put in your mouth without a condom?

_____

_____ Refuse to answer

19. How many times did a man put his mouth on your penis?

_____ [IF 0, GO TO Q 22]

_____ Refuse to answer

20. How many times did a man put his mouth on your penis without a condom?

_____ [IF 0, GO TO Q 22]

_____ Refuse to answer

21. How many men put their mouths on your penis without a condom?

_____

_____ Refuse to answer

SEXUAL BEHAVIOR WITH WOMEN

I will now ask you questions about your sexual behavior with women.

22. During the past three months, how many female sexual partners have you had?

_____ [IF 0, SKIP QUESTIONS ON SEX WITH WOMEN AND GO TO NEXT SECTION]

_____ Refuse to answer

22x. You responded Refuse to answer for the previous question. Is it true you are unwilling to answer questions about female partners?

1. Yes, I refuse to answer questions about female sexual partners
2. No, I am willing to answer questions about female sexual partners

Of these, how many do you consider to be ...(Please put a number in each box. Enter 0 (zero) if none. Your answers must add up to _____ [CASI PROGRAMMER: ENTER NUMBER FROM Q22]):

22A.1 lovers (women with whom you've felt emotionally involved in a committed relationship and with whom you had sex - like a spouse, fiancée, or girlfriend)

_____

22A.2 one-night stands (women with whom you had sex only once)

_____

22A.3 other female partners (women with whom you had sex who are neither your lovers nor one-night stands)

_____

22AX.1 Refuse to answer

Vaginal Intercourse
In the past three months.....

23. How many times did you put your **penis** in a **vagina**?

_____ [IF 0, GO TO Q 30]

_____ Refuse to answer

24. How many times did you put your **penis** in a **vagina** <u>without</u> a condom?

_____ [IF 0, GO TO Q 30]

_____ Refuse to answer

25. Into <u>how many women's</u> **vagina**s did you put your **penis** <u>without</u> a condom?

_____

_____ Refuse to answer

[CASI, IF Q 25 = 1 (I.E., THE PARTICIPANT REPORTS THAT HE PENETRATED ONLY ONE WOMAN WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 26; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 27]

You said you put your penis in one woman's vagina without a condom.

26. Regarding this woman (please select one answer).....
___ 1. This woman told you she was HIV negative and you had no reason to doubt it.
___ 2. You knew this woman was HIV positive.
___ 3. You were not completely sure of this woman's HIV status.
___ 4. Refuse to answer

[CASI, IF Q 25 IS 2 OR MORE (I.E., THE PARTICIPANT REPORTS THAT HE PENETRATED TWO OR MORE WOMEN WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 27; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 30]

You said you put your penis in ___ women's [CASI CAN INSERT THE NUMBER FROM THE PREVIOUS QUESTION (Q 25)] vaginas without a condom.

27.1 (27.) Of those women, how many had actually told you they were HIV-negative and you had no reasons to doubt it?

_____

27.2 (28.) Of those women, how many do you know to be HIV-positive?

_____

27.3 (29.) How many were you NOT completely sure about their HIV status?

_____

27X.1 Refuse to answer

Anal Intercourse
In the past three months.....

30. How many times did you put your penis in a woman's rectum?

_____ [IF 0, GO TO Q 37]

_____ Refuse to answer

31. How many times did you put your penis in a woman's rectum without a condom?

_____ [IF 0, GO TO Q 37]

_____ Refuse to answer

32. Into how many women's rectums did you put your penis without a condom?

_____

_____ Refuse to answer

[CASI, IF Q 32 = 1 (I.E., THE PARTICIPANT REPORTS THAT HE PENETRATED ONLY ONE WOMAN IN THE RECTUM WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 33; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 34]

You said you put your penis in one woman's rectum without a condom.

33. Regarding this woman (please select one answer).....
___ 1. This woman told you she was HIV negative and you had no reason to doubt it.
___ 2. You knew this woman was HIV positive.
___ 3. You were not completely sure of this woman's HIV status.
___ 4. Refuse to answer

[CASI, IF Q 32 IS 2 OR MORE (I.E., THE PARTICIPANT REPORTS THAT HE PENETRATED TWO OR MORE WOMEN IN THE RECTUM WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 34; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 37]

You said you put your penis in ____ women's [CASI CAN INSERT THE NUMBER FROM THE PREVIOUS QUESTION (Q 32)] rectums without a condom.

34.1 (34.) Of those women, how many had actually told you they were HIV-negative and you had no reasons to doubt it?

_____

_____ Refuse to answer

34.2 (35.) Of those women, how many do you know to be HIV-positive?

_____

_____ Refuse to answer

34.3 (36.) How many were you NOT completely sure about their HIV status?

_____

34X.1 Refuse to answer

Oral Sex

In the past three months.....

37. How many times did you put your mouth on a vagina?

_____ [IF 0, GO TO 39]

_____ Refuse to answer

38. How many women's vaginas did you put your mouth on?

_____

_____ Refuse to answer

39. How many times did a woman put her mouth on your penis?

_____ [IF 0, GO TO NEXT SECTION]

_____ Refuse to answer

40. How many times did a woman put her mouth on your penis without a condom?

_____ [IF 0, GO TO NEXT SECTION]

_____ Refuse to answer

41. How many women put their mouths on your penis without a condom?

_____

_____ Refuse to answer

SECTION B.2 SEXUAL BEHAVIOR [WOMEN - IF ANSWER TO Q A.6 = 2]

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **901** IN THIS SECTION.

The following questions refer to your sexual behavior during the past three months that is, from [CASI: INSERT TODAY'S DATE THREE MONTHS AGO] until today.

Sometimes talking about sex can be confusing because people have so many different words to describe body parts and sexual activities. Before we start, we're going to take a minute to review some words so it is clear what we are asking.

[SCREEN TIPS WILL BE GENERATED FOR WORDS IN BOLD TO DISPLAY THEIR MEANINGS AND ALTERNATE PHRASES, AS PER THE FOLLOWING:]

Penis is the male sex organ. Some people call it "dick" or "cock."

Vagina is the female sex organ. Some people call it "pussy."

Rectum and anus are frequently called "butt" or "asshole."

Anal intercourse is when a man puts his penis in another man's or a woman's rectum or anus; some people call this "butt fucking."

Vaginal intercourse is when a man puts his penis into a woman's vagina; some people call this "fucking" or "screwing" or "having sex."

Oral sex is when people put their mouths or tongues on each other's sex organs. When someone does this to a man's penis, some people call this a "blow job." When someone does this to a woman's vagina, some people call this "going down on her."

As you go through the following questions, these words will sometimes appear in bold. If you are not sure what a word in bold means, use the mouse to place the arrow or cursor on the bolded word to see its meaning.

Since the focus will be exclusively on anal, vaginal or oral sex, do *NOT* include in your answers references to partners with whom you did not engage in anal, vaginal, or oral sex.

SEXUAL BEHAVIOR WITH MEN

First, I will ask you about your sexual behavior with men.

1. During the past three months, how many male sexual partners have you had?

_____ [IF 0, SKIP QUESTIONS ON SEX WITH MEN AND GO TO QUESTIONS ON SEX WITH WOMEN.]

_____ Refuse to answer

1x. You responded Refuse to answer for the previous question. Is it true you are unwilling to answer questions about male partners?
1. Yes, I refuse to answer questions about male sexual partners
2. No, I am willing to answer questions about male sexual partners

Of these, how many do you consider to be ...(Please put a number in each box. Enter 0 (zero) if none. Your answers must add up to _____ [CASI PROGRAMMER: ENTER NUMBER FROM Q1]):

1A.1 lovers (men with whom you've felt emotionally involved in a committed relationship and with whom you had sex - like a spouse or husband, fiancé, or boyfriend)
_____

1A.2 one-night stands (men with whom you had sex only once)
_____

1A.3 other male partners (men with whom you had sex who are neither your lovers nor one-night stands) [SKIP TO Q 2]
_____

1AX.1 Refuse to answer

Vaginal Intercourse

In the past three months.....

2. How many times did a male partner put his **penis** in your **vagina**?

_____ [IF 0, GO TO Q 9]

_____ Refuse to answer

3. How many times did a male partner put his **penis** in your **vagina** without a condom?

_____ [IF 0, GO TO Q 9]

_____ Refuse to answer

4. How many men put their **penis**es in your **vagina** without a condom?

_____

_____ Refuse to answer

[IF Q 4 = 1 (I.E., THE PARTICIPANT REPORTS THAT ONLY ONE MAN PENETRATED HER VAGINA WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 5; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 6]

You said that one man put his penis in your vagina without a condom.

5. Regarding this man (please select one answer).....
___ 1. This man told you he was HIV negative and you had no reason to doubt it.
___ 2. You knew this man was HIV positive.
___ 3. You were not completely sure of this man's HIV status.
___ 4. Refuse to answer

[IF Q 4 IS 2 OR MORE (I.E., THE PARTICIPANT REPORTS THAT TWO OR MORE MEN PENETRATED HER VAGINA WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 6; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 9]

You said ___ men [INSERT THE NUMBER FROM THE PREVIOUS QUESTION (Q 4)] put their penises in your vagina without a condom.

6.1 (6.) Of those men, how many had actually told you they were HIV-negative and you had no reasons to doubt it?

_____

6.2 (7.) Of those men, how many do you know to be HIV-positive?

_____

6.3 (8.) How many were you NOT completely sure about their HIV status?

_____

6X.1 Refuse to answer

Anal Intercourse

In the past three months.....

9. How many times did a male partner put his **penis** in your **rectum**?

_____ [IF 0, GO TO Q 16.]

[CASI PROGRAMMER: IF RESPONSE IS “0”, ALSO SKIP QUESTIONS IN SECTION D (LUBRICANT USE), WHICH ARE CONTINGENT ON RAI IN THE PAST 3 MONTHS.]

_____ Refuse to answer

10. How many times did a male partner put his **penis** in your **rectum** without a condom?

_____ [IF 0, GO TO Q 16.]

_____ Refuse to answer

[CASI PROGRAMMER: IF RESPONSE IS "0", ALSO SKIP QUESTIONS B IN SECTION F (SUBSTANCE USE), WHICH ARE CONTINGENT ON URAI IN THE PAST 3 MONTHS.]

11. How many men put their **penis**es in your **rectum** without a condom?

_____

_____ Refuse to answer

[IF Q 11 = 1 (I.E., THE PARTICIPANT REPORTS THAT ONLY ONE MAN PENETRATED HER RECTUM WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 12; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 13]

You said that one man put his penis in your rectum without a condom.

12. Regarding this man (please select one answer).....
___ 1. This man told you he was HIV negative and you had no reason to doubt it.
___ 2. You knew this man was HIV positive.
___ 3. You were not completely sure of this man's HIV status.
___ 4. Refuse to answer

[IF Q 11 IS 2 OR MORE (I.E., THE PARTICIPANT REPORTS THAT TWO OR MORE MEN PENETRATED HER RECTUM WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 13; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 16]

You said ___ men [INSERT THE NUMBER FROM THE PREVIOUS QUESTION (Q 11)] put their penises in your rectum without a condom.

13.1 (13.) Of those men, how many had actually told you they were HIV-negative and you had no reasons to doubt it?

_____

13.2 (14.) Of those men, how many do you know to be HIV-positive?

_____

13.3 (15.) How many were you NOT completely sure about their HIV status?

_____

13X.1 Refuse to answer

Oral Sex

In the past three months.....

16. How many times did you put a man's penis in your mouth?

_____ [IF 0, GO TO Q 19]

_____ Refuse to answer

17. How many times did you put a man's penis in your mouth without a condom?

_____ [IF 0, GO TO Q 19]

_____ Refuse to answer

18. How many men's penises did you put in your mouth without a condom?

_____

_____ Refuse to answer

19. How many times did a man put his mouth or tongue on your vagina?

_____ [IF 0, GO TO Q 21]

_____ Refuse to answer

20. How many men put their mouths on your vagina?

_____

_____ Refuse to answer

SEXUAL BEHAVIOR WITH WOMEN

I will now ask you questions about your sexual behavior with women.

21. During the past three months, how many female sexual partners have you had?

_____ [IF 0, SKIP QUESTIONS ON SEX WITH WOMEN AND GO TO NEXT SECTION]
_____ Refuse to answer

21x. You responded Refuse to answer for the previous question. Is it true you are unwilling to answer questions about female partners?
1. _____ Yes, I refuse to answer questions about female sexual partners
2. _____ No, I am willing to answer questions about female sexual partners

Of these, how many do you consider to be...(Please put a number in each box. Enter 0 (zero) if none. Your answers must add up to _____ [CASI PROGRAMMER: ENTER NUMBER FROM Q21]):

21A.1 lovers (women with whom you've felt emotionally involved in a committed relationship and with whom you had sex - like a spouse equivalent or girlfriend)
_____

21A.2 one-night stands (women with whom you had sex only once)
_____

21A.3 other female partners (women with whom you had sex who are neither your lovers nor one-night stands) [SKIP TO Q 22]
_____

21AX.1 Refuse to answer

Receptive Anal Intercourse

In the past three months.....

22. How many times did you and your female partner(s) share any toys or other objects (e.g., vibrators, dildos, etc.) to penetrate each other in the rectum?

_____

_____ Refuse to answer

Oral Sex

In the past three months.....

23. How many times did you put your mouth on a vagina?

_____ [IF 0, GO TO 25]

_____ Refuse to answer

24. How many women's vaginas did you put your mouth on?

_____

_____ Refuse to answer

25. How many times did a woman put her mouth on your vagina?

_____ [IF 0, GO TO NEXT SECTION]

_____ Refuse to answer

26. How many women put their mouths on your vagina?

_____

_____ Refuse to answer

SECTION C.1 RECTAL DOUCHING

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **601** IN THIS SECTION, UNLESS OTHERWISE NOTED.

The following questions refer to rectal douching.

For clarity, we will define a few terms.

[HYPERLINKS WILL BE GENERATED FOR WORDS IN BOLD TO DISPLAY THEIR MEANINGS AND ALTERNATE PHRASES, AS PER THE FOLLOWING:]

A rectal douche, or enema, refers to water or a prepared liquid or substance that is inserted in your rectum or ass to clean it.

Receptive anal intercourse, or receptive anal sex, is when a man puts his penis in your rectum, or his dick in your ass. Some people call this being butt fucked or bottoming.

Remember, if you are not sure what a word in bold means, use the mouse to place the arrow or cursor on the word to see its meaning.

1. How many times did you use a **rectal douche** in the past 3 (three) months?

___ ___ ___ [IF '0,' GO TO NEXT SECTION]

_____ Refuse to answer [901]

2a. Of the times you used a **rectal douche** in the past 3 months, how many times did you douche for general hygiene?

___ ___ ___

_____ Refuse to answer

2b. Of the times you used a **rectal douche** in the past 3 months, how many times did you douche in preparation for **receptive anal intercourse**?

___ ___ ___

_____ Refuse to answer

2c. Of the times you used a **rectal douche** in the past 3 months, how many times did you douche following **receptive anal intercourse**?

___ ___ ___

_____ Refuse to answer

2d. Of the times you used a **rectal douche** in the past 3 months, how many times did you douche for pleasure?

___ ___ ___

_____ Refuse to answer

2e. Of the times you used a **rectal douche** in the past 3 months, how many times did you douche when constipated?

___ ___ ___

_____ Refuse to answer

2f. Of the times you used a **rectal douche** in the past 3 months, how many times did you douche when ill?

___ ___ ___

_____ Refuse to answer

2g. Of the times you used a **rectal douche** in the past 3 months, how many times did you douche for some other reason? (First, please specify the other reason) _____

Number of times (please enter 0 if no other reason is specified): ___ ___ ___

_____ Refuse to answer

[IF Q 2.b > 0 , ASK Q 3, 4, 5, AND 6. OTHERWISE, GO TO INSTRUCTIONS ABOVE Q 7.]

3. At what age did you use a **rectal douche** before **receptive anal intercourse** for the first time?

___ ___ Years

_____ Refuse to answer [100]

4. What made you use a **rectal douche** before **receptive anal intercourse**? [Indicate all that apply]

___ 1. To be clean
___ 2. My sex partner suggested it
___ 3. My friends talked about it
___ 4. Other: _____
___ 5. Refuse to aswer

5. How frequently do you give yourself a rectal douche before receptive anal intercourse?

1. Always
2. Frequently
3. Infrequently
4. Refuse to answer

6. Typically, how long before receptive anal intercourse do you use a rectal douche?

1. Less than 30 minutes
2. 30 minutes to 1 hour
3. Between 1 and 2 hours
4. Between 2 and 3 hours
5. Between 3 and 4 hours
6. 4 hours or more
7. Refuse to answer

[IF Q 2.c > 0, ASK Q 7, 8, 9, AND 10. OTHERWISE, GO TO Q11.]

7. At what age did you use a rectal douche after receptive anal intercourse for the <u>first</u> time?

_____ Years

_____ Refuse to answer [100]

8. What made you use a rectal douche after receptive anal intercourse? [Indicate all that apply]

___ 1. To be clean
___ 2. To prevent getting any sexually transmitted infections, including HIV, from my sex partner
___ 3. My sex partner suggested it
___ 4. My friends talked about it
___ 5. Other (specify): _____
___ 6.Refuse to answer

9. How frequently do you give yourself a rectal douche after receptive anal intercourse?
1. Always
2. Frequently
3. Infrequently
4. Refuse to answer

10. Typically, how long after receptive anal intercourse do you use a rectal douche (in minutes)?

___ ___ minutes [_____ Refuse to answer [999]

11a. When you used a rectal douche in the past 3 (three) months, how many times did you use <u>a hose apparatus that was a non-disposable douche or enema bag system (neoprene or rubber bag, rubber hose, plastic clamp, and plastic or rubber nozzle)</u>?

___ ___ ___

_____ Refuse to answer

11b. When you used a rectal douche in the past 3 (three) months, how many times did you use <u>a hose apparatus that was a shower head hose and nozzle?</u>

___ ___ ___

_____ Refuse to answer

11c. When you used a rectal douche in the past 3 (three) months, how many times did you use <u>a hose apparatus that was a “sinker”, a portable rubber or vinyl hose that attaches to a sink?</u>

___ ___ ___

_____ Refuse to answer

11d. When you used a rectal douche in the past 3 (three) months, how many times did you use a pre-packaged bulb apparatus that was an over-the-counter disposable enema product (e.g., Fleet®)?

___ ___ ___

_____ Refuse to answer

11e. When you used a rectal douche in the past 3 (three) months, how many times did you use a pre-packaged bulb apparatus that was a re-usable bulb enema?

___ ___ ___

_____ Refuse to answer

11f. When you used a rectal douche in the past 3 (three) months, how many times did you use some other kind of applicator? (First, please specify what other kind of applicator you used):
_____

Number of times (please enter 0 if no other applicator is specified):___ ___

_____ Refuse to answer

[IF Q 11A > 0, ASK Q12. OTHERWISE GO TO INSTRUCTION ABOVE Q13.]

12. When you use a rectal douche with a hose apparatus, how long do you usually run the water?
    1. 15 seconds or less
    2. 16 seconds to 1 minute
    3. Between 1 and 4 minutes
    4. 5 minutes or more
    5. Refuse to answer

[IF Q 11B > 0, ASK Q13. OTHERWISE GO TO Q14.]

13. Each time you use a rectal douche that is a pre-packaged product, do you typically go through your rectal douching procedure once or more than once?
    1. Once
    2. More than once
    3. Refuse to answer

14. Please estimate how far into your rectum you typically insert the applicator?
    1. up to 1 inch
    2. between 1 and 2 inches
    3. between 2 and 3 inches
    4. more than 3 inches
    5. Refuse to answer

15. Where do you typically use a rectal douche?

1. Toilet
2. Shower/tub
3. Sink
4. Other (specify): _____
5. Refuse to answer

16. Tell me about the temperature you prefer…
    1. Hot
    2. Warm
    3. Cool
    4. No preference
    5. Refuse to answer

17. In what position do you typically prefer to use a rectal douche?
    1. Kneeling
    2. Laying on side
    3. Standing
    4. Squatting or seated over toilet/tub
    5. Other (specify): _____
    6. Refuse to answer

18. Have you ever had an injury as a result of rectal douching?
    1. No [GO TO Q 21]
    2. Yes
    3. Refuse to answer

19. How many times have you had an injury to the anus or rectum while douching in the past 3 months?
    _____ [IF "0," GO TO Q 21]

    _____ Refuse to answer

20. When injuries have occurred, what was the cause? [Indicate all that apply]
    ____ 1. Problems with the nozzle
    ____ 2. Position played a role
    ____ 3. Problems with the product
    ____ 4. Other: _____
    ____ 5. Refuse to answer

21. Do you get cramps or any other kind of discomfort when you use a rectal douche?
    1. Always
    2. Frequently
    3. Infrequently
    4. Never
    5. Refuse to answer

22. When you use a rectal douche, how long does it usually take you before you have a bowel movement?
    1. Occurs immediately
    2. 1-5 minutes
    3. More than 5 minutes
    4. Refuse to answer

SECTION C.2 VAGINAL DOUCHING [WOMEN - IF ANSWER TO Q A.6 = 2]

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **601** IN THIS SECTION, UNLESS OTHERWISE NOTED.

The following questions refer to use of vaginal douches.

For clarity, we will define a few terms.

[HYPERLINKS WILL BE GENERATED FOR WORDS IN BOLD TO DISPLAY THEIR MEANINGS AND ALTERNATE PHRASES, AS PER THE FOLLOWING:]

A vaginal douche refers to water or a prepared liquid or substance that is inserted in your vagina to clean it**.**

Vaginal intercourse is when a man puts his penis in your vagina. This is often called "having sex" or "fucking."

Remember, if you are not sure what a word in bold means, use the mouse to place the arrow or cursor on the word to see its meaning.

1. How many times did you use a **vaginal douche** in the past 3 (three) months?

_____ [IF '0,' GO TO NEXT SECTION]

_____ Refuse to answer [901]

2a. Of the times you used a **vaginal douche** in the past 3 months, how many times did you douche for general hygiene?

___ ___ ___

_____ Refuse to answer

2b. Of the times you used a **vaginal douche** in the past 3 months, how many times did you douche in preparation for **vaginal intercourse**?

___ ___ ___

_____ Refuse to answer

2c. Of the times you used a **vaginal douche** in the past 3 months, how many times did you douche following **vaginal intercourse**?

___ ___ ___

_____ Refuse to answer

2d. Of the times you used a **vaginal douche** in the past 3 months, how many times did you douche for pleasure?

___ ___ ___

_____ Refuse to answer

2e. Of the times you used a **vaginal douche** in the past 3 months, how many times did you douche for some other reason? (First, please specify the other reason) _____

Number of times (please enter 0 if no other reason is specified): ___ ___ ___

_____ Refuse to answer

[IF Q 2.b > 0 , ASK Q3, 4, 5, AND 6. OTHERWISE, GO TO INSTRUCTION ABOVE Q7.]

3. At what age did you use a **vaginal douche** before **vaginal intercourse** for the first time?

_____ Years

_____ Refuse to answer [100]

4. What made you use a vaginal douche before vaginal intercourse? [Indicate all that apply]

___ 1. To be clean
___ 2. My sex partner suggested it
___ 3. My friends talked about it
___ 4. Other: _____
___ 5. Refuse to answer

5. How frequently do you give yourself a vaginal douche before vaginal intercourse?
1. Always
2. Frequently
3. Infrequently
4. Refuse to answer

6. Typically, how long before vaginal intercourse do you use a vaginal douche?
1. Less than 30 minutes
2. 30 minutes to 1 hour
3. Between 1 and 2 hours
4. Between 2 and 3 hours
5. Between 3 and 4 hours
6. 4 hours or more
7. Refuse to answer

[IF Q 2.c > 0, ASK Q 7, 8, 9, AND 10. OTHERWISE, GO TO Q11.]

7. At what age did you use a vaginal douche after vaginal intercourse for the first time?

_____ Years

_____ Refuse to answer [100]

8. What made you use a vaginal douche after vaginal intercourse? [Indicate all that apply]
___ 1. To be clean

___ 2. To prevent getting any sexually transmitted infections, including HIV, from my sex partner
___ 3. My sex partner suggested it
___ 4. My friends talked about it
___ 5. Other: _____
___ 6. Refuse to answer

9. How frequently do you give yourself a vaginal douche after vaginal intercourse?
1. Always
2. Frequently
3. Infrequently
4. Refuse to answer

10. Typically, how long after vaginal intercourse do you use a vaginal douche? (in minutes)

___ ___ minutes [99=MISSING]

_____ Refuse to answer [999]

11a. When you used a vaginal douche in the past 3 (three) months, how many times did you use a hand-held hose or bidet?

___ ___

_____ Refuse to answer

11b. When you used a vaginal douche in the past 3 (three) months, how many times did you use over-the-counter disposable douche products (e.g., Massengill® or Summer's Eve®)?

___ ___

_____ Refuse to answer

11c. When you used a vaginal douche in the past 3 (three) months, how many times did you use Re-usable bottle system?

___ ___

_____ Refuse to answer

11d. When you used a vaginal douche in the past 3 (three) months, how many times did you use some other kind of applicator? (First, please specify what other kind of applicator you used):
_____

Number of times (please enter 0 if no other applicator is specified): ___ ___

_____ Refuse to answer

[IF Q 11A > 0, ASK Q12. OTHERWISE GO TO INSTRUCTION ABOVE Q13.]

12. When you use a vaginal douche with a hose apparatus, how long do you usually run the water?
    1. 15 seconds or less
    2. 16 seconds to 1 minute
    3. Between 1 and 4 minutes
    4. 5 minutes or more
    5. Refuse to answer

[IF Q 11B or 11C > 0, ASK Q13. OTHERWISE GO TO 14.]

13. Each time you use a vaginal douche with a bottle-type product, do you typically go through your douching procedure once or more than once?
    1. Once
    2. More than once
    3. Refuse to answer

14. Please estimate how far into your vagina you typically insert the applicator?
    1. up to 1 inch
    2. between 1 and 2 inches
    3. between 2 and 3 inches
    4. more than 3 inches
    5. Refuse to answer

15. Where do you typically use a vaginal douche?
    1. Toilet
    2. Shower/tub
    3. Sink
    4. Other (specify): _____
    5. Refuse to answer

16. Tell me about the temperature you prefer…
    1. Hot
    2. Warm
    3. Cool
    4. No preference
    5. Refuse to answer

17. In what position do you typically prefer to use a vaginal douche?
    1. Kneeling
    2. Laying on side
    3. Standing
    4. Squatting or seated over toilet/tub
    5. Other (specify): _____
    6. Refuse to answer

18. Have you ever had an injury as a result of using a vaginal douche?
    1. No [GO TO Q 21]
    2. Yes
    3. Refuse to answer

19. How many times have you had an injury to the vagina while douching in the past 3 months?
    _____ [IF "0," GO TO Q 21]

_____ Refuse to answer

20. When injuries have occurred, what was the cause? [Indicate all that apply]
    ____ 1. Problems with the nozzle
    ____ 2. Position played a role
    ____ 3. Problems with the product
    ____ 4. Other: _____
    ____ 5. Refuse to answer

21. Do you get cramps or any other kind of discomfort when you use a vaginal douche?
    1 Always
    2. Frequently
    3. Infrequently
    4. Never
    5. Refuse to answer

SECTION D. LUBRICANT USE FOR RAI

The following questions refer to commercial sexual lubricants. This does not include saliva or the lubricant that comes with condoms.

Remember, if you are not sure what a word in bold means, use the mouse to place the arrow or cursor on the word to see its meaning.

1 During the past three months, how frequently have you had **receptive anal intercourse** using a commercial sexual lubricant?

_____ 1 Never [ASK Q 2 AND SKIP TO NEXT SECTION]
_____ 2 Sometimes [ASK Q 2 AND CONTINUE WITH THIS SECTION]
_____ 3 Always [SKIP Q 2 AND GO TO Q 3]
_____ 4 Refuse to answer

2 During the past three months, when you did NOT use a rectal lubricant for **receptive anal intercourse**, why was that the case? [Indicate all that apply] [IF Q 1 = 0, ASK THIS QUESTION AND SKIP TO NEXT SECTION; OTHERWISE GO TO Q 3]

_____ 1 Sometimes I prefer dry sex
_____ 2 I disliked the lubricant
_____ 3 I used saliva
_____ 4 I used condoms with lubricant
_____ 5 Lubricant was not available
_____ 6 I was in a rush
_____ 7 I couldn't afford to buy it
_____ 8 My partner refused
_____ 9 Other (specify): _____
_____ 10 Refuse to answer

3 What types of lubricant do you use? [Indicate all that apply]

_____ 1 Silicon-based (e.g., Eros)
_____ 2 Water-based (e.g., KY, Wet)
_____ 3 Oil-based (e.g., Crisco)
_____ 4 Refuse to answer

4 During **receptive anal intercourse**, how much commercial lubricant do you use <u>on average</u>?

_____ 1 5 ml or less (1 teaspoon)
_____ 2 About 10 ml (2 teaspoons)
_____ 3 About 15 ml (3 teaspoons)
_____ 4 About 30 ml (6 teaspoons)
_____ 5 About 50 ml (10 teaspoons)
_____ 6 Refuse to answer

5 Where do you <u>usually</u> get your lubricant from?

_____ 1 Sex shop

_____ 2 Pharmacy/drug store
_____ 3 AIDS Agency
_____ 4 Bar, disco, sex club
_____ 5 Online
_____ 6 Other (specify): _____
_____ 7 Refuse to answer

6 Do you prefer a lubricant with …
_____ 1 No flavor
_____ 2 Flavor
_____ 3 It doesn't matter
_____ 4 Refuse to answer

7 Do you prefer a lubricant with …
_____ 1 No color/transparent
_____ 2 Color
_____ 3 It doesn't matter
_____ 4 Refuse to answer

8 Do you prefer a lubricant with …
_____ 1 Unscented/ No scent
_____ 2 Scented
_____ 3 It doesn't matter
_____ 4 Refuse to answer

9 In terms of commercial lubricant consistency, what do you prefer?
_____ 1 Very liquid
_____ 2 Somewhat liquid
_____ 3 Neither
_____ 4 Somewhat thick
_____ 5 Very thick
_____ 6 Refuse to answer

10 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 (specify): _____
_____ 8 Refuse to answer

11 In general when you have receptive 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 rectum?
_____ 4 Inside the condom?
_____ 5 On the outside of the condom?
_____ 6 Other (specify):_____
_____ 7 Refuse to answer

12 When you are having receptive anal intercourse, who applies the lubricant?
_____ 1 Self
_____ 2 Partner
_____ 3 Both
_____ 4 Refuse to answer

13 When is the lubricant first applied?
_____ 1 Before there is any sexual contact
_____ 2 During sex but before he penetrates you
_____ 3 After he first penetrates you if you feel the need for it
_____ 4 Refuse to answer

14 How frequently do you usually reapply the commercial lubricant during receptive anal intercourse?
_____ 1 Never
_____ 2 Once
_____ 3 Twice
_____ 4 3 times or more
_____ 5 Refuse to answer

15 From your past experience, does the application of the lubricant interrupt sex?
_____ 1 It does not interrupt sex
_____ 2 It interrupts sex but does not bother me
_____ 3 It interrupts sex and bothers me
_____ 4 Refuse to answer

SECTION E. NONOXYNOL-9

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **999** IN THIS SECTION.

The following questions refer to Nonoxynol-9 or N-9.

1. Have you ever heard of Nonoxynol-9 or N-9?
   1. No or not sure [SKIP TO NEXT SECTION]
   2. Yes
   3. Refuse to answer

2. When you choose a lubricant, do you check if it contains Nonoxynol-9 or N-9?
   1. Never
   2. Infrequently
   3. Frequently
   4. Always
   5. Refuse to answer

3. Have you ever used a lubricant containing Nonoxynol-9 or N-9 for anal sex, either with or without condoms?
   1. No [SKIP TO Q.5]
   2. Yes
   3. I don't know [SKIP TO Q.5]
   4. Refuse to answer

4a. In the past three months, did you use lubricants containing Nonoxynol-9 or N-9 for anal sex, either with or without condoms?

_____ Yes

_____ No [SKIP TO Q.5]

_____ I don't know [SKIP TO Q.5]

_____ Refuse to answer

4b. In the past three months, how many times have you used lubricants containing Nonoxynol-9 or N-9 for anal sex, either with or without condoms?

_____ # OF TIMES

_____ I don't know

_____ Refuse to answer

Please indicate your level of agreement with the following statements. [ALLOW ONLY ONE ANSWER PER QUESTION.]

		Strongly Agree	Moderately Agree	Mildly Agree	Mildly Disagree	Moderately Disagree	Strongly Disagree	I don't know	Refuse to Answer
5_r1.	Using a lubricant containing Nonoxynol-9 or N-9 during anal sex will prevent HIV transmission.	1	2	3	4	5	6	7	8
5_r2.	Using a lubricant containing Nonoxynol-9 or N-9 will irritate or injure a person's rectal tissue.	1	2	3	4	5	6	7	8
5_r3.	Using a lubricant containing Nonoxynol-9 or N-9 during anal sex will increase the risk of getting HIV.	1	2	3	4	5	6	7	8

SECTION F. SUBSTANCE USE

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **999** IN THIS SECTION.

The following questions refer to alcohol and drug use. Have you ever used…[R1]

	EVER USED?			**[A]** FREQUENCY PAST 3 MONTHS	**[B]** FREQUENCY WITH URAI PAST 3 MONTHS
	No	**Yes**	**Refuse to answer**		
1. Alcohol?	1	2	3		
2. Marijuana/hashish?	1	2	3		
3. Ecstasy/MDMA?	1	2	3		
4. Crystal Meth/Amphetamines/ Methamphetamines/Speed/Crank?	1	2	3		
5. Ketamine/Special K?	1	2	3		
6. GHB (Gamma Hydroxybutyrate)?	1	2	3		
7. Other Hallucinogens/LSD/ Mushrooms?	1	2	3		
8. Poppers/Amyl Nitrite/Butyl Nitrite?	1	2	3		
9. Crack?	1	2	3		
10. Cocaine (not Crack)?	1	2	3		
11. Heroin?	1	2	3		
12. Viagra, Cialis, or Levitra?	1	2	3		
13. Other pharmaceutical drugs not prescribed to you by a physician (Percocet or similar drugs)?	1	2	3		

Now using the following response choices, please indicate:

1 = Never
2 = Once a month or less
3 = 2-3 times a month
4 = About once a week
5 = 2-6 times a week
6 = About once a day
7 = More than once a day
8 = Refuse to answer

[R1] This does not show up as a table on the screen but as individual questions.

[PRESENT ONE SUBSTANCE AT A TIME. QUESTIONS C, D AND E APPLY ONLY TO ALCOHOL USE]

A. How often have you used _____ during the past three months? [IF "1" FOR ALCOHOL USE, SKIP B, C, D AND E; IF "1" FOR ALL OTHER SUBSTANCES, SKIP B]

_____ Refuse to answer

B. In the past three months, how often have you used _____ immediately before or during <u>unprotected</u> receptive anal intercourse?

_____ Refuse to answer

[QUESTIONS C, D AND E APPLY ONLY TO ALCOHOL USE; INSERT QUESTIONS C, D AND E IMMEDIATELY AFTER ALCOHOL QUESTIONS]

C. During the past three months, about how many glasses of beer or wine did you usually have on the days that you drank?

_____ glasses of beer or wine/day

_____ Refuse to answer

D. During the past three months, about how many shots of liquor did you usually have on the days that you drank?

_____ shots of liquor/day

_____ Refuse to answer

E. Thinking about the times you used alcohol during the last three months, how much did you typically use?

___ 1. Too little to feel any effect
___ 2. Enough to feel it a little
___ 3. Enough to feel it a lot
___ 4. Enough to get drunk
___ 5. Enough to feel like you might pass out
___ 6. Refuse to answer

ASK Q 14 AFTER ALL SUBSTANCE QUESTIONS.

14. In the past three months, how many times did you inject any non-prescribed drugs into your veins or under your skin?

_____

_____ Refuse to answer

SECTION G. HIV Testing

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **999** IN THIS SECTION, UNLESS OTHERWISE NOTED.

I would now like to ask you a few questions about your HIV status. I remind you that this information is completely confidential.

1. How many times in total have you been tested for HIV?

   __ __

   _____ Refuse to answer [101]

2. When were you first tested for HIV?

   ____/_____ mm yyyy

   _____ Don't know / Refuse to answer

3. When were you last tested for HIV?

   ____/_____
   mm yyyy

   _____ Don't know / Refuse to answer

4. How many times, of those you have been tested for HIV, have you been notified of the test results?

   [0] None

   ____ [IF "0" OR LESS THAN THE # OF TIMES REPORTED IN Q 1, ASK Q 6; OTHERWISE SKIP TO Q 7]

_____Refuse to answer

5. When you did not receive the test results, why was that the case? [Indicate all that apply]

   ____ 1 Fear of finding out the results
   ____ 2 Fear that Immigration and Naturalization Services (INS) will find out the results
   ____ 3 Required for work (e.g., the military)
   ____ 4 Concern that my sexual partners may be contacted
   ____ 5 I just assumed I was negative
   ____ 6 I would have been called if my test result was positive
   ____ 7 Other: _____
   ____ 8 Refuse to answer

6. Have you ever tested HIV positive?

   [1] No
   [2] Yes
   [3] Refuse to answer

SECTION H. RECTAL MICROBICIDE INTENTIONS

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **98** IN THIS SECTION.

Scientists are trying to develop alternatives to condoms for the prevention of HIV transmission during intercourse. Microbicides could be one such alternative.

Remember, if you are not sure what a word in bold means, use the mouse to place the arrow or cursor on the word to see its meaning.

1. If a rectal microbicide were available that provided some protection against HIV, and it came in the form of a gel (microbicidal gel), how likely would you be to use it every time you have **receptive anal intercourse**?

   1—2—3—4—5—6—7—8—9—10
   Extremely Unlikely — Extremely Likely

   Refuse to answer

2. How likely would you be to use it every time you have **receptive anal intercourse** with a **lover**?

   1—2—3—4—5—6—7—8—9—10
   Extremely Unlikely — Extremely Likely

   Refuse to answer

3. How likely would you be to use a microbicidal gel every time you have **receptive anal intercourse** with a **one-night stand**?

   1—2—3—4—5—6—7—8—9—10
   Extremely Unlikely — Extremely Likely

   Refuse to answer

4. How likely would you be to use a microbicidal gel every time you have **receptive anal intercourse** with other partners, men who were neither your **lover**s nor **one-night stand**s?

   1—2—3—4—5—6—7—8—9—10
   Extremely Unlikely — Extremely Likely

   Refuse to answer

5. How likely would you be to use a microbicidal gel for receptive anal intercourse if you were using alcohol or drugs?

   1—2—3—4—5—6—7—8—9—10

Extremely Unlikely — Extremely Likely

Refuse to answer

6. If a rectal microbicide were available that provided some protection against HIV, and it came in the form of a suppository, how likely would you be to use it every time you have receptive anal intercourse?

1—2—3—4—5—6—7—8—9—10
Extremely Unlikely — Extremely Likely

Refuse to answer

7. If a rectal microbicide were available that provided some protection against HIV, and it came in the form of an enema, how likely would you be to use it every time you have receptive anal intercourse?

1—2—3—4—5—6—7—8—9—10
Extremely Unlikely — Extremely Likely

Refuse to answer

SECTION I. PEP/PREP

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **98** IN THIS SECTION.

PEP

Another HIV-prevention method that is being explored is called Post Exposure Prophylaxis, also known as PEP or "morning after pill(s)." People who may have been exposed to HIV take pills after the fact to avoid, or at least decrease, the chances of becoming infected, although the ability of this method to prevent sexually transmitted HIV-infections in humans has not been clearly demonstrated.

1. Have you heard about post-exposure prophylaxis (PEP) before?
   ____ 1. No [GO TO Q 4]
   ____ 2. Yes
   ____ 3. Refuse to answer

2. When did you first hear about PEP?

   ____/_____
   mm yyyy

   _____ Don't Know / Refuse to answer

3. How did you first hear about PEP? Was it through…[Indicate all that apply]
   ____ 1. A friend
   ____ 2. The media
   ____ 3. A medical provider
   ____ 4. A sex partner
   ____ 5. Online
   ____ 6. Other (please specify)_____
   ____ 7. Refuse to answer

4. How likely would you be to use PEP if you suspected you may have been exposed to HIV?

   1——2——3——4——5——6——7——8——9——10
   Extremely Unlikely — Extremely Likely

   11. Refuse to answer

5. Have you ever taken any medication after a risky sexual encounter with the expectation of getting protection against HIV?
   ____ 1. No [GO TO Q 8]
   ____ 2. Yes
   ____ 3. Refuse to answer

6. What medication did you take?

   _____

   _____ Refuse to answer

7. How did you get it?
____ 1. Physician
____ 2. Friend
____ 3. Over the Internet
____ 4. Other: _____
____ 5. Refuse to answer

8. Do you have any friends who have taken any medication after a risky sexual encounter with the expectation of getting protection against HIV?
____ 1. No
____ 2. Yes
____ 3. Not sure
____ 4. Refuse to answer

PREP

Another HIV-prevention method being studied is called Pre-Exposure Prophylaxis, or PREP. People who use Pre-Exposure Prophylaxis, or PREP might have to take a pill either every day or at least a couple of hours prior to sex, to counteract or at least decrease the chances of becoming infected if they came in contact with HIV.

9. Have you heard about pre-exposure prophylaxis (PREP) before?
____ 1. No [GO TO Q 12]
____ 2. Yes
____ 3. Refuse to answer

10. When did you first hear about PREP?

____/_____
mm yyyy

_____ Don't know / Refuse to answer

11. How did you first hear about PREP? Was it through… [Indicate all that apply]
____ 1. A friend
____ 2. The media
____ 3. A medical provider
____ 4. A sex partner
____ 5. Online
____ 6. Other _____
____ 7. Refuse to answer

12. If PREP were available, how likely would you be to use it?

1—2—3—4—5—6—7—8—9—10
Extremely Unlikely — Extremely Likely

11. Refuse to answer

13. Although there is no evidence that taking medication before sex may prevent someone from catching HIV, some men do it. Have you ever taken any medication before having sex as protection against HIV?

____ 1. No [GO TO Q 16]
____ 2. Yes
____ 3. Refuse to answer

14. What medication did you take?

_____

_____ Refuse to answer

15. How did you get it?
____ 1. Physician
____ 2. Friend
____ 3. Over the Internet
____ 4. Other: _____
____ 5. Refuse to answer

16. Do you have any friends who take medication before having sex as protection against HIV?
____ 1. No
____ 2. Yes
____ 3. Not sure
____ 4. Refuse to answer

Please indicate your agreement to the following statements.

17. I would not take anti-HIV drugs because I am concerned about their side effects.
1. Strongly Agree
2. Agree
3. Disagree
4. Strongly Disagree
5. Refuse to answer

18. I would know how to get anti-HIV drugs if I wanted them.
1. Strongly Agree
2. Agree
3. Disagree
4. Strongly Disagree
5. Refuse to answer

19. I could not afford anti-HIV drugs.
1. Strongly Agree
2. Agree
3. Disagree
4. Strongly Disagree
5. Refuse to answer

Section II: Phone Reporting System

THE COMPUTERIZED SYSTEM WILL POSE THE FOLLOWING QUESTIONS:

Hi!

Please enter your User ID
Please enter your PIN number

[INSTRUCTIONS: "Please wait to enter your response to a question until it is completely asked. If you need the question repeated, just wait a few seconds."

1. Since your last call, how many times have you used the gel? Use the touchpad to enter the number of times. [IF 1 OR MORE, SKIP 2; IF 0 ASK 2 AND 3 AND SKIP TO 6]
2. Since your last call, have you had any problems that prevented you from using the gel? Press 1 for yes, 2 or no. [IF 1, GO TO 2a]
   2a. [PROMPT TO RECORD PROBLEM] Please tell us briefly about any problem you had.
3. Since your last call, have you used a douche or enema, or put any object other than the gel inside your anus? (Y/N) [IF 1, GO TO 3a]
   3a. [PROMPT TO RECORD WHAT WAS USED] Please tell us briefly what you inserted in your anus.
4. At what time did you last use the gel? Use the touchpad to enter the hour and minutes. For example, if you used the gel at 1:30am, press zero, one, three, zero and then you'll be asked to indicate if this was am or pm. Enter the 4 digit time you applied the gel using the keypad on your phone
   4a. Press 1 for AM or 2 for PM
5. Have you had any problems using the gel since your last call? (Y/N) [IF 1, GO TO 5a]
   5a. [PROMPT TO RECORD PROBLEM] Please tell us briefly about any problem you had.
6. Since your last call, have you had receptive anal intercourse? (Y/N) [IF 1, GO TO 6a; IF 2, GO TO 14]
   6a. Since your last call, how many times have you had receptive anal intercourse? Use the touchpad to enter the number of times. [DO NOT ALLOW "0" AS A RESPONSE FOR Q6a]
7. The last time you had receptive anal intercourse, was it your first time with this partner? (Y/N)
8. Did your partner have a condom on when he inserted his penis into your rectum?
   1. If he had a condom on all of the time, press 1
   2. If he had a condom on part of the time, press 2
   3. If he never had a condom on, press 3 [IF 3, GO TO 10]
9. Did your partner use the condoms they gave you for the study when he inserted his penis in your rectum? (Y/N; "I don't know")
10. Since your last call, did you have gel inside your rectum every time you had receptive anal intercourse?
    1. If you had the gel inside your rectum every time, press 1
    2. If you had the gel inside your rectum some of the time, press 2
    3. If you never had the gel inside your rectum, press 3 [IF 3, GO TO 14]
11. Did your partner know you were using the gel? (Y/N) [IF NO, GO TO 14]
12. What was your partner's reaction to the gel? Enter 1 for "he liked it," 2 for "he neither liked it nor disliked it," and 3 for "he disliked it."

13. Since your last call, has your partner complained or said anything negative about using the gel? (Y/N)
14. Did you have any problems calling this phone system? (Y/N) [IF 1, GO TO 14a]
    14a. [PROMPT PARTICIPANT TO RECORD A RESPONSE] Specify the problems you had calling the phone system.
15. Did you have any problem entering your information into this phone system? (Y/N) [IF 1, GO TO 15a]
    15a. [PROMPT PARTICIPANT TO RECORD A RESPONSE] Specify the problems you had entering information into the phone system.
16. Do you have any comments? (Y/N) [IF 1, GO TO 16a]
    16a. [PROMPT PARTICIPANT TO RECORD A RESPONSE] What would you like to inform the study staff about?

You have received $2 for completing this call for a total of [$2 x number of days during which a call was received]. If you continue to call every day, you will receive a $10 bonus. You have until midnight of every day to call. If you forget to call, you will still get the full amount you have accumulated with each call but you won't get the additional $10 bonus. You have completed the call. Thank you.

Section III: Product Acceptability Questionnaire

Product Acceptability Questionnaire

TEXT IN CAPITAL LETTERS SHOULD NOT BE PRESENTED TO THE PARTICIPANT.

PRESENT PRACTICE QUESTIONS USED IN THE BASELINE QUESTIONNAIRE

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. [*Question 1*]

Click the "NEXT" button to go to the next screen.

Introduction *[Question 2]*
Good! You can always move to the next screen by clicking "next", or, to go to the previous screen, click on the browser's "back" arrow at the top of the screen.
Click the "NEXT" button to go to the next screen.

****

Practice *[Question 3]*

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]
3.1 Eggs
3.2 Cheese
3.3 Croutons
3.4 Salad Dressing
3.5 Carrots
3.6 Bacon bits
3.7 None of the above

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 4]*

Do you like summer?
Yes
No
Refuse to answer

This is an example of a single response question:
If you want to change your response, simply click the response you want.

****

****

Practice *[Question 5]*

This question shows how to use your mouse to scroll over a word to see its meaning or alternate phrases. Use the mouse to put the arrow or cursor on the word in bold in the following sentence:

[SCREEN TIPS WILL BE GENERATED FOR WORDS IN BOLD TO DISPLAY THEIR MEANINGS AND ALTERNATE PHRASES, AS PER THE FOLLOWING:]

How many times have you eaten **dessert [SCREEN TIP: SWEETS, ICE CREAM, CAKE, CHOCOLATE]** in the past five days?

For questions that ask the number of times, if you are unsure just give your best estimate.

****

Practice *[Question 6]*

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:

In general, how much do you like ice cream?

1——2——3——4——5——6——7——8——9——10

Dislike very much — Like very much

11- Refuse to answer

****

Ok. If you had any problem answering the prior questions, let the study staff know about it. Otherwise, click “NEXT” and proceed with the questionnaire.

SECTION J. PRODUCT ACCEPTABILITY

1. Overall, how much did you like the gel?

1——2——3——4——5——6——7——8——9——10
Disliked very much — Liked very much

11. Refuse to answer

2. How much did you like the color of the gel?

1——2——3——4——5——6——7——8——9——10
Disliked very much — Liked very much

11. Refuse to answer
12. Don't know, I did not see the gel

3. How much did you like the taste of the gel?

1——2——3——4——5——6——7——8——9——10
Disliked very much — Liked very much

11. Refuse to answer
12. Don't know, I did not taste the gel

4. How much did you like the scent of the gel?

1——2——3——4——5——6——7——8——9——10
Disliked very much — Liked very much

11. Refuse to answer
12. Don't know, I did not smell the gel

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 very much — Liked very much

11. Refuse to answer

6. How much did you like how the gel felt inside your rectum immediately after inserting it?

1——2——3——4——5——6——7——8——9——10
Disliked very much — Liked very much

11. Refuse to answer

7. How much did you like how the gel felt inside your rectum 30 minutes after inserting it?

1——2——3——4——5——6——7——8——9——10
Disliked very much — Liked very much

11. Refuse to answer

SECTION K. APPLICATION PROCESS

Now we would like to ask you some questions about applying the gel.

1. Overall, how much did you like the process of applying the gel?

1—2—3—4—5—6—7—8—9—10
Disliked very much — Liked Very much

11. Refuse to answer

2. How easy were the instructions to follow in order to apply the gel?

1—2—3—4—5—6—7—8—9—10
Very difficult — Very Easy

11. Refuse to answer

3. How easy was it to handle the applicator while trying to insert the gel?

1—2—3—4—5—6—7—8—9—10
Very difficult — Very Easy

11. Refuse to answer

4. How easy was it to insert the gel?

1—2—3—4—5—6—7—8—9—10
Very difficult — Very Easy

11. Refuse to answer

5. Where were you at the time you applied the gel?
   1. Bathroom
   2. Bedroom
   3. Other: _____
   4. Refuse to answer

6. What position did you typically use to apply the gel? (Check all that apply.)
   1. Kneeling
   2. Laying on side
   3. Standing
   4. Squatting or seated over toilet or tub
   5. Other: _____
   6. Refuse to answer

SECTION L. APPLICATOR

Now we would like to ask you some questions about the applicator.

1. How much did you like the gel applicator?

1	2	3	4	5	6	7	8	9	10
Disliked very much									Liked very much

11. Refuse to answer

2. Did you have any problems with the tip used to deliver the gel in your rectum?
   1. No
   2. Yes Please specify what problems:_____
   3. Refuse to answer

3. How easy would it be to carry this gel applicator around if you needed to?

1	2	3	4	5	6	7	8	9	10
Extremely difficult									Extremely easy

11. Refuse to answer

SECTION M. CHANGES IN HYGIENE DUE TO PRODUCT USE

Now we would like to ask you some questions about how you used the gel.

1. Thinking about all of the episodes of gel use, how often did you douche or give yourself an enema prior to inserting the gel?
    1. None of the occasions
    2. A few of the occasions
    3. Some of the occasions
    4. Most of the occasions
    5. All occasions
    6. Refuse to answer

2. Did your douching practices change as a result of using the gel?

    1. No, I douched as frequently as I typically do [SKIP TO Q 4]
    2. Yes, I douched less frequently than I typically do
    3. Yes, I douched more frequently than I typically do
    4. Not applicable, I never douche [SKIP TO Q 4]
    5. Refuse to answer

3. Why did your douching practices change when you used the gel? _____

4. Did you ever use less than the specified amount of gel during the occasions of gel use?
    1. No [SKIP TO NEXT SECTION]
    2. Yes
    3. Refuse to answer

5. On how many occasions did you use less than the specified amount of gel?
    1. On one of the occasions
    2. A few of the occasions
    3. Some of the occasions
    4. Most of the occasions
    5. All occasions
    6. Refuse to answer

6. When you used less than indicated, about how much did you use?
    1. Three quarters of the applicator
    2. Half of the applicator
    3. One quarter of the applicator
    4. Refuse to answer

7. Please indicate the reason why you used less than the specified amount of gel?
    _____

SECTION N. EXPERIENCES USING THE GEL

Now we would like to ask you some questions about problems you may have experienced when using the gel.

1. Thinking about your experiences using the gel, did you experience any leakage?
   1. None [SKIP TO Q 3]
   2. Some
   3. A lot
   4. Refuse to answer

2. How much were you bothered by leakage?

1	2	3	4	5	6	7	8	9	10
Not at all									Very much

   11. Refuse to answer

3. Did you experience any soiling of your underwear or bed sheets?
   1. None [SKIP TO Q 5]
   2. Some
   3. A lot
   4. Refuse to answer

4. How much were you bothered by soiling of underwear or bed sheets?

1	2	3	4	5	6	7	8	9	10
Not at all									Very much

   11. Refuse to answer

5. Did you experience any bloating as a result of using the gel?
   1. None [SKIP TO Q 7]
   2. Some
   3. A lot
   4. Refuse to answer

6. How much were you bothered by the bloating?

1	2	3	4	5	6	7	8	9	10
Not at all									Very much

   11. Refuse to answer

7. Did you experience any gassiness as a result of using the gel?
   1. None [SKIP TO Q 9]
   2. Some
   3. A lot
   4. Refuse to answer

8. How much were you bothered by gassiness?

1——2——3——4——5——6——7——8——9——10
Not at all — Very much

11. Refuse to answer

9. Did you experience any stomach cramps as a result of using the gel?
   1. None [SKIP TO Q 11]
   2. Some
   3. A lot
   4. Refuse to answer

10. How much were you bothered by the stomach cramps?

1——2——3——4——5——6——7——8——9——10
Not at all — Very much

11. Refuse to answer

11. Did you experience the urge to have a bowel movement as a result of using the gel?
   1. None [SKIP TO Q 13]
   2. Some
   3. A lot
   4. Refuse to answer

12. How much were you bothered by the urge to have a bowel movement?

1——2——3——4——5——6——7——8——9——10
Not at all — Very much

11. Refuse to answer

13. Did you experience any diarrhea as a result of using the gel?
   1. None [SKIP TO Q 15]
   2. Some
   3. A lot
   4. Refuse to answer

14. How much were you bothered by the diarrhea?

1——2——3——4——5——6——7——8——9——10
Not at all — Very much

11. Refuse to answer

15. Did you experience any pain or trauma caused by applying this product?
   1. None [SKIP TO Q 17]

2. Some
3. A lot
4. Refuse to answer

16. How much were you bothered by the pain or trauma?

1——2——3——4——5——6——7——8——9——10
Not at all — Very Much

11. Refuse to answer

17. Did you have the feeling that the gel was absorbed by your gut after you had it in for a while?
    1. None
    2. Some
    3. A lot
    4. Refuse to answer

18. Did the gel feel cold to you?
    1. No [SKIP TO Q 20]
    2. Yes
    3. Refuse to answer

19. How much were you bothered by the gel feeling cold?

1——2——3——4——5——6——7——8——9——10
Not at all — Very Much

11. Refuse to answer

20. Did the gel feel sticky to you?
    1. No [SKIP TO NEXT SECTION
    2. Yes
    3. Refuse to answer

21. How much were you bothered by the gel feeling sticky?

1——2——3——4——5——6——7——8——9——10
Not at all — Very Much

11. Refuse to answer

SECTION O. POSSIBILITY OF COVERT USE

Let's briefly go over the definitions of some terms so that you understand what is being asked.

Lovers are men with whom you've felt emotionally involved in a committed relationship and with whom you had sex - like a spouse, spouse equivalent, fiancé, or boyfriend.

One-night stands are men with whom you had sex only once.

Other male partners are men with whom you had sex who are neither lovers nor one-night stands.

1. If you have a lover(s), would you want to use this gel without his (their) knowledge?
    1. No [SKIP TO Q 3]
    2. Yes
    3. N/A, I don't have a lover [SKIP TO Q 4]
    4. Refuse to answer

2. Under what circumstances would you use this gel without your lover's knowledge?

_____

3. Would it be possible to use this gel without your lover(s) noticing it?
    1. No
    2. Yes
    3. Refuse to answer

Remember, if you are not sure what a word in bold means, use the mouse to place the arrow or cursor on the word to see its meaning.

4. If you have one-night stand(s), would you want to use this gel without his (their) knowledge?
    1. No [SKIP TO Q 6]
    2. Yes
    3. N/A, I don't have one-night stands [SKIP TO Q 7]
    4. Refuse to answer

5. Under what circumstances would you use this gel without one-night stands' knowledge?

_____

6. Would it be possible to use this gel without one-night stand(s) noticing it?
    1. No
    2. Yes
    3. Refuse to answer

7. If you have other male sexual partner(s), men who were neither lovers nor one-night stands, would you want to use this gel without his (their) knowledge?
    1. No [SKIP TO Q 9]
    2. Yes
    3. N/A, I don't have other male sexual partner(s) [SKIP TO NEXT SECTION]
    4. Refuse to answer

8. Under what circumstances would you use this gel without your other male partners' knowledge?

_____

9. Would it be possible to use this gel without your other male partner(s) noticing it?
    1. No
    2. Yes
    3. Refuse to answer

SECTION P. INTENTION TO USE PRODUCT IN THE FUTURE

Now we would like to ask you about your intentions to use the gel in the future.

1. If a rectal microbicide were available that provided some protection against HIV, and it looked like the gel you have used in this study, how likely would you be to use it (a microbicidal gel) every time you have **receptive anal intercourse**?

1——2——3——4——5——6——7——8——9——10
Extremely Unlikely — Extremely Likely

98. Refuse to answer

2. How likely would you be to use a microbicidal gel every time you have **receptive anal intercourse** with a **lover**?

1——2——3——4——5——6——7——8——9——10
Extremely Unlikely — Extremely Likely

98. Refuse to answer

3. How likely would you be to use a microbicidal gel every time you have **receptive anal intercourse** with a **one-night stand**?

1——2——3——4——5——6——7——8——9——10
Extremely Unlikely — Extremely Likely

98. Refuse to answer

4. How likely would you be to use a microbicidal gel every time you have receptive anal intercourse with <u>other male partners</u>, men who were neither lovers nor one-night stands?

1——2——3——4——5——6——7——8——9——10
Extremely Unlikely — Extremely Likely

98. Refuse to answer

5. How likely would you be to use a microbicidal gel on the occasions when you don't use condoms?

1——2——3——4——5——6——7——8——9——10
Extremely Unlikely — Extremely Likely

98. Refuse to answer

6. How likely would you be to use a microbicidal gel if you had to wait 30 minutes after application before having intercourse?

1——2——3——4——5——6——7——8——9——10
Extremely Unlikely — Extremely Likely

98. Refuse to answer

7. How likely would you be to use a microbicidal gel every time you have receptive anal intercourse if you were using drugs or alcohol?

1——2——3——4——5——6——7——8——9——10
Extremely Unlikely — Extremely Likely

98. Refuse to answer

8. How much would you be willing to spend on a microbicidal gel per sexual occasion?
    1. About as much as one spends for condoms
    2. Twice as much as one spends for condoms
    3. Three times as much
    4. Other: _____
    5. Refuse to answer

SECTION Q. WILLINGNESS TO USE HIGHER VOLUME

Now, we do not yet know the amount of microbicidal gel that would be necessary to provide protection against the HIV virus during sex.

1. Thinking about the amount of gel you used, would you be willing to use the product if half as much of the amount you used was required?
    1. No
    2. Yes
    3. Refuse to answer

2. Would you be willing to use the product if twice as much of the amount you used was required?
    1. No
    2. Yes
    3. Refuse to answer

SECTION R. RECOMMENDATIONS

Please help us understand how we could make the gel more attractive to people like you.

1. Would you change anything about the tip of the applicator?
    1. No
    2. Yes (Please specify what you would change:)_____
    3. Refuse to answer

2. Would you change anything about the gel's scent?
    1. No
    2. Yes (Please specify what you would change:)_____
    3. Don't know, I did not smell the gel
    4. Refuse to answer

3. Would you change anything about the gel's taste?
    1. No
    2. Yes (Please specify what you would change:)_____
    3. Don't know, I did not taste the gel
    4. Refuse to answer

4. Would you change anything about the gel's color?
    1. No
    2. Yes (Please specify what you would change:)_____
    3. Don't know, I did not see the gel
    4. Refuse to answer

5. Would you change anything about the consistency of the gel (how thick or thin it is)?
    1. No
    2. Yes (Please specify what you would change:)_____
    3. Refuse to answer

6. Would you change anything about how the product is packaged?
    1. No
    2. Yes (Please specify what you would change:)_____
    3. Refuse to answer

7. Would you recommend the product be…
    1. Refillable
    2. Disposable
    3. Refuse to answer

8. If you have any other recommendations, please write your recommendations below.

    _____

    _____

    _____