MTN-012/IPM 010 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	1.0	18MAR11	First final version
2	Protocol	1.0	18MAR11	First final version
3	Documentation Requirements	1.0	18MAR11	First final version
4	Participant Accrual and Enrollment	1.0	18MAR11	First final version
5	Participant Follow-Up and Visit Checklists	1.0	18MAR11	First final version
6	Participant Retention	1.0	18MAR11	First final version
7	Study Product Considerations For Non-Pharmacy Staff	1.0	18MAR11	First final version
8	Clinical Considerations and Safety Monitoring	1.0	18MAR11	First final version
9	Laboratory Considerations	1.1	14APR11	Updated required amount for plasma archive (10ml EDTA tube to yield at least 4ml of plasma)
10	Data Collection	1.0	18MAR11	First final version
11	Data Communiqués	1.0	18MAR11	First final version
12	CASI Users Manual	1.0	18MAR11	First final version
13	Study Reporting Plan	1.0	18MAR11	First final version

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Section 1. Introduction

This section specifies the sources of procedural information available to MTN-012/IPM 010 study staff, the responsibilities of MTN-012/IPM 010 Investigators of Record (IoRs), and the process by which each study site is approved to begin implementation of MTN-012/IPM 010.

1.1 Sources of Procedural Information

All study procedures must be conducted in accordance with the MTN-012/IPM 010 protocol. 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-012/IPM 010 Study Management Team (described below) of any such inconsistencies.

Study implementation questions that are not answered by the protocol, or this manual, should be directed to the MTN-012/IPM 010 Study Management Team. This group consists of representatives of the MTN Coordinating and Operations Center (CORE; FHI), Statistical and Data Management Center (SDMC), Network Laboratory (NL), and the MTN Pharmacist, and can be reached using the following email address:

mtn012mgmt@mtnstopshiv.org

Per the specifications of Section 8 of this manual, questions related to participant clinical eligibility, study product use management, adverse event reporting, and adverse event management should be directed to the MTN-012/IPM 010 Protocol Safety Physicians using the following email address:

mtn012safetymd@mtnstopshiv.org

1.2 Investigator Responsibilities

MTN-012/IPM 010 must be conducted in accordance with the United States Code of Federal Regulations and the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice. Copies of these regulations and guidelines are referenced in the MTN Manual of Operations (MOP) which can be accessed at:

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

The DAIDS policies on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* and *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies can be accessed at:

http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch

MTN-012/IPM 010 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. Copies of all such regulations, policies, and guidelines should be maintained in on-site essential document files (see also Section 3.1 of this manual).

The IoR at each site must sign both a protocol signature page and an FDA Form 1572 to formally indicate his/her agreement to conduct MTN-012/IPM 010 in accordance with the study protocol and all applicable regulations, policies, and guidelines. The protocol signature page can be found 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. IoRs may delegate their obligations and responsibilities for conducting MTN-012/IPM 010 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 the period of study implementation.

Consistent with the regulations, guidelines, and policies cited above, the IoR at each site must obtain and maintain institutional review board and/or ethics committee (IRB/EC) approval of MTN-012/IPM 010 throughout the period of study implementation. See Section 8.4 of the MTN MOP for detailed information on IRB/EC submission, review, approval, and documentation requirements. All sites are encouraged to request an acknowledgement of receipt for all documents submitted to their IRBs/ECs and to request that IRBs/ECs note the effective and expiry dates of all approvals. Documentation of all correspondence to and from all responsible IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files.

1.3 Study Activation Process

Prior to undertaking any study procedures, each site must obtain approval to conduct MTN-012/IPM 010 from all responsible regulatory authorities and IRBs/ECs. Each site also must complete protocol registration procedures with the DAIDS Regulatory Support Center Protocol Registration Office and study activation procedures with DAIDS, FHI, SDMC, NL, and the MTN Pharmacist. Detailed information on the requirements of these pre-implementation steps can be found in Section 10 of the MTN MOP. 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.

Section 2. Protocol

This section contains a complete reference copy of the MTN-012/IPM 010 protocol. At the time of this printing, protocol Version 1.0, dated 29 November 2010, and Letter of Amendment (LoA) #01, dated 11 February 2011, reflect current protocol specifications.

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

- Upon receipt of any protocol clarification memos, add a copy of the memo to this section.
- Upon receipt of any additional letters of amendment, add a copy of the letter of amendment to this section.
- Upon receipt of any full protocol amendments, replace the contents of this section with the amended protocol.

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.

LETTER OF AMENDMENT #01 TO:

MTN-012/IPM 010
DAIDS Document ID: 11771

Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

Version 1.0 / 29 November 2010

IND# 69,022

Letter of Amendment Date: February 11, 2011

Instructions to Study Sites from the Division of AIDS

The following information impacts the MTN-012/IPM 010 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

The following information will also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. An LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-012/IPM 010. This LoA includes changes to the following items:

1. Updates to Section 5.3, *Exclusion Criteria*, to reflect the Cockcroft-Gault formula for males.
2. Updates to Section 6.7, *Study Product Adherence*; Section 7.2, *Enrollment*; Section 7.9, *Behavioral Assessments*; Appendix I and the *Enrollment Sample Informed Consents*; to indicate that the Phone Reporting System will not be used to collect adherence data during the study.
3. Section 7.6, *Interim Visit*, Table 11: *Interim Visit* updated to indicate that participants will be counseled regarding product use instructions, if indicated.
4. Updates to the Protocol Team Roster.
5. List of Abbreviations and Acronyms has been updated.

Implementation

This LoA is official MTN-012/IPM 010 protocol documentation. Prior to implementing the revisions listed below, the MTN-012/IPM 010 study sites will submit this LoA to all relevant regulatory authorities and the IRB/EC. Upon receipt of all required regulatory and IRB/EC approvals, the protocol revisions listed below will be implemented. With the exception of protocol roster changes, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions

1. The following update was made to Section 5.3, *Exclusion Criteria*, j., vi., to reflect the Cockcroft-Gault formula for males.

   Calculated creatinine clearance less than 80 mL/min by the Cockcroft-Gault formula ~~where creatinine clearance in mL/min= (140-age in years) X (weight in kg) x 0.85/72 x serum creatinine in mg/dL.~~ **for males."**

2. The following changes are made to Section 6.7, *Study Product Adherence*; Section 7.2, *Enrollment*; Section 7.9, *Behavioral Assessments*; Appendix I: *Schedule of Study Visits and Evaluations* and Appendix IV: *Enrollment Sample Informed Consents*; to indicate that the Phone Reporting System will not be used to collect adherence data during the study.

   Section 6.7, Study Product Adherence Counseling and Assessment, second paragraph:

   Participants will be instructed to apply the product daily before bedtime, usually in the evening or before longest period of rest, which is expected to result in better adherence. To monitor adherence, participants will be asked to ~~use a phone reporting system (PRS) immediately 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 or PTID), and then~~ respond to ~~pre-recorded~~ questions on product use ~~since last call~~ and adherence to protocol guidelines on product use **at the Final Clinic/Termination Visit**. ~~Responses to the PRS can be entered by either pressing keys (i.e., 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 will then contact the participant to inquire about missed calls (e.g., if the participant forgot to call) and adherence to the study product regimen. Thus, this system allows monitoring of the reporting on adherence to the PRS on a time-stamped basis. Given that participants are instructed to use the product prior to their longest period of rest and to call the system immediately after applying the product, the calls are a proxy for compliance with time of application. There will be a recall question on adherence (How many times did you apply the gel on your penis during the days of the trial?) at the Final Clinic/Termination Visit. However, the answer to this question will only be used to replace PRS reporting in the case that PRS data is completely missing.~~ In addition, participants will be asked to return both used and unused applicators and these applicators will be documented by study staff.

   Section 7.2, Enrollment (Day 0), Table 8, Behavioral Component:

   Table 8: Enrollment Visit (Day 0)

Visit 2: Enrollment Visit	
Component	Procedures
Behavioral	• ~~Provide instructions on use of Phone Reporting System (PRS) to participants~~

   Section 7.9, Behavioral Assessments, first sentence:

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

   Section 7.9, Behavioral Assessments, Adherence Questionnaire and Product Acceptability Questionnaire Sections:

   ~~Adherence Questionnaire~~
   ~~Adherence will be assessed with the PRS which participants will be asked to call daily. Responses to specific questions on product use since the prior call (e.g., "Did you use the product? Y/N) will constitute~~

~~one measure of adherence. In addition, at the Final Visit, participants will be asked to report on study product use during the trial via the self-interview.~~

Product Acceptability **and Adherence** Questionnaire
This self-interview will be completed by participants at the Final Clinic Visit. This tool includes structured and semi-structured questions about experiences the participant had using the gel, likes and dislikes concerning the gel, any changes he may have introduced or may wish to introduce in the product used, any problems he may have had or product side-effects (and how much the participant was bothered by them), and likelihood of using a microbicide in the future. **Adherence will be measured by a recall question on adherence (How many times did you apply the gel on your penis during the days of the trial?) and questions related to missed doses at the Final Clinic/Termination Visit.** It is anticipated that the Product Acceptability **and Adherence** Questionnaire will include a few questions similar to those asked on the Baseline Behavioral Assessment so that responses may be compared (i.e. anticipated likelihood of product use).

Appendix I: Schedule of Study Visits and Evaluations, Behavioral Assessments section:

~~Instructions on use of Phone Reporting System~~		~~X~~			

Appendix IV: Sample Informed Consent, Enrollment, What do I have to do if I am in this study?

- ~~Receive instructions about how to call an automated phone system each time you use the gel at home. 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.~~

Appendix IV: Sample Informed Consent, Enrollment, Will I receive any payment?

WILL I RECEIVE ANY PAYMENT?
You will be compensated for your time and effort for your scheduled study visits ~~and phone calls~~. You will receive [SITE TO INSERT – SPECIFIC AMOUNT OF MONEY] for each visit. ~~You will receive [SITE TO INSERT – SPECIFIC AMOUNT OF MONEY] for each phone call~~. 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].

3. Section 7.6*, Interim Visit*, Table 11: *Interim Visit* has been updated to eliminate the redundancy in the Clinical Component section of the Interim Visit. This update still allows participants to be counseled at the Interim Visit regarding product use instructions, if indicated:

Interim Visit	
Component	Procedures
Clinical	• ~~Product use instructions*~~

4. The following updates are made to the Protocol Team Roster:

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Removed:

Rebecca Giguere, MPH
Joseph Romano, PhD

5. The List of Abbreviations and Acronyms is updated:

~~PRS Phone Reporting System~~

The above information will be incorporated into the next version of the protocol at a later time if it is amended.

MTN-012/IPM 010

Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

Microbicide Trials Network

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

Grant #:
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DAIDS Protocol #: 11771

IND Sponsor:
International Partnership for Microbicides

IPM IND# 69,022

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CONFIDENTIAL

Version 1.0

November 29, 2010

MTN-012/IPM 010

Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
ALT	alanine transaminase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
BRWG	Behavioral Research Working Group
CAB	Community Advisory Board
CASI	computer assisted self-interview
CBC	Complete Blood Count
CDC	(US) Centers for Disease Control
CFR	Code of Federal Regulations
CORE	Coordinating and Operations Center
CRF	case report form
CT	*Chlamydia trachomatis,* Chlamydia
CTA	Clinical Trial Agreement
CWG	community working group
DAERS	Division of AIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAIDS PRO	Division of AIDS Protocol Registration Office
DAPY	di-amino-pyrimidine
DLV	delavirdine
EAE	expedited adverse event
EC	Ethics Committee
EFV	efavirenz
GC	*Neisseria gonorrhoeae,* gonorrhea
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
HEC	hydroxyethylcellulose
HHS	Health and Human Services
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus-Type 1
HPTN	HIV Prevention Trials Network
HSV	herpes simplex virus
HSV-2	herpes simplex virus-type 2
hu-PBL	human peripheral blood lymphocytes
hu-SCID	humanized severe combined immunodeficient
IATA	International Air Transport Association
ICF	Informed Consent Form

IFA	Immunofluorescence Assay
IND	Investigational New Drug
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
K_a	absorption rate
K_e	elimination rate
Kg	kilogram
LDMS	Laboratory Data Management System
mg	milligram
MDP	Microbicides Development Programme
mL	milliliter
mm	millimeter
MPA	medroxyprogesterone acetate
MTN	Microbicide Trials Network
MTT	[1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan]
NAAT	nucleic acid amplification test
NF	National Formulary
ng	nanogram
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NL	Network Laboratory
nM	nanomolar
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NVP	nevirapine
OHRP	Office for Human Research Protections
PBS	phosphate-buffered saline
PEP	post-exposure prophylaxis
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development, Inc.
PRS	Phone Reporting System
PSRT	Protocol Safety Review Team
PTID	participant identification
RE	Regulatory Entity
RNA	ribonucleic acid
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SDMC	Statistical Data Management Center
SHIV	simian human immunodeficiency virus
SMC	Study Monitoring Committee
SOP	standard operating procedure(s)

SSP	study specific procedure(s)
STI	sexually transmitted infection
TEAE	treatment-emergent adverse event
UA	urinalysis
ULN	upper limits of normal
US FDA	United States Food and Drug Administration
USP	United States Pharmacopoeia
WB	Western Blot
wt	wild-type
µg	microgram

MTN-012/IPM 010

Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

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MTN-012/IPM 010

Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

INVESTIGATOR SIGNATURE FORM

Version 1.0

November 29, 2010

A Study of the Microbicide Trials Network

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

IND Sponsor:
International Partnership for Microbicides

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 each of the three study products for the indication in which they were 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 and International Partnership for Microbicides (IPM) policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, NIMH, and IPM for review prior to submission for publication.

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-012/IPM 010

Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

PROTOCOL SUMMARY

Short Title:	Male Tolerance of Dapivirine Gel
Clinical Phase:	Phase 1
IND Sponsor:	International Partnership for Microbicides
Protocol Chair:	Ross D. Cranston MD, FRCP
Sample Size:	Approximately 48 males (24 circumcised and 24 uncircumcised)
Study Population:	Healthy, HIV-negative, circumcised and uncircumcised men at least 18 years of age
Study Sites:	US sites selected by the MTN Executive Committee
Study Design:	Phase 1, randomized (2:1:1), double-blind, multi-site, placebo-controlled trial
Study Duration:	Approximately 8 days per participant, with a projected accrual period of approximately 8-12 weeks
Study Products:	Dapivirine gel (0.05%) Matched placebo gel Universal Placebo gel
Study Regimen:	Study participants will apply study gel to the penis once daily for 7 days

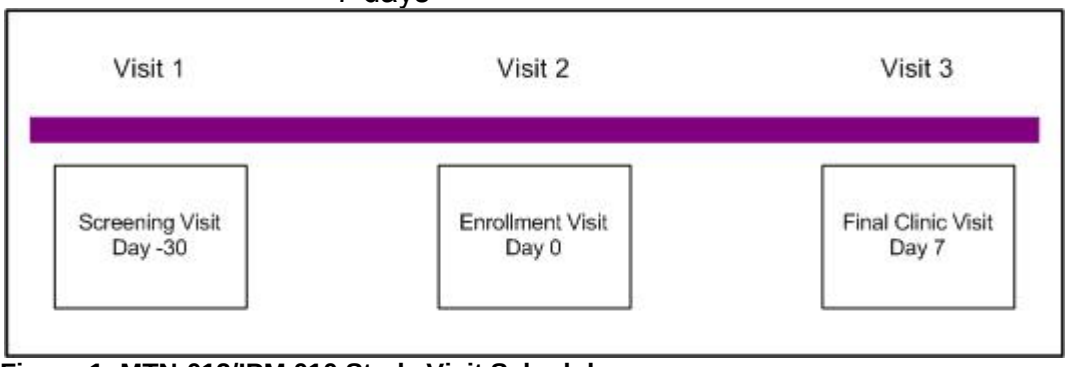


Figure 1: MTN-012/IPM 010 Study Visit Schedule

Primary Objectives:

- To determine the genitourinary safety of dapivirine gel (0.05%) compared to matched placebo gel and Universal Placebo gel following seven once daily penile applications

Primary Endpoints:

- Any evidence of Grade 2 or higher male genitourinary adverse event(s) as defined by the DAIDS Adverse Event (AE) Grading Table Version 1.0, December 2004 (Clarification dated August 2009), Addendum 2 (Male Genital Toxicity Table for Use in Topical Microbicide Studies)

Secondary Objectives:

- To assess the pharmacokinetics in plasma following 7 days of once daily penile application of dapivirine gel (0.05%)

- To assess the systemic safety following 7 days of once daily penile application of dapivirine gel (0.05%)

- To assess the acceptability following 7 days of once daily penile application of dapivirine gel (0.05%)

Secondary Endpoints:

- Dapivirine concentrations in blood

- Grade 2 or higher clinical and laboratory adverse events as defined by the DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009) and the Male Genital Toxicity Table for Use in Topical Microbicide Studies

- 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 sexual intercourse in the future

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures
Protocol Number:	MTN-012/IPM 010
Short Title:	Male Tolerance of Dapivirine Gel
Date:	November 29, 2010

1.2 Sponsor and Monitor Identification

Funded by:	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 Dr. Bethesda, MD 20892 USA
IND Sponsor:	International Partnership for Microbicides 8401 Colesville Rd., Suite 200 Silver Spring, MD 20910 USA
Monitor:	Pharmaceutical Product Development (PPD), Inc 929 North Front St. Wilmington, NC 28401-3331 USA

1.3 Medical Officer

Medical Officer:	Lydia E. Soto-Torres, MD, MPH 6700 B Rockledge Dr. Bethesda, MD 20892-7628 USA

1.4 Clinical Laboratories

Network:	MTN Network Laboratory 204 Craft Ave. Pittsburgh, PA 15213 USA
Pharmacokinetics:	PRA International - Early Development Services Bioanalytical Laboratory Westerbrink 3

9405 BJ Assen
Netherlands

1.5 Data Center

Data Center: Statistical Center for HIV/AIDS Research & Prevention (SCHARP)- Fred Hutchinson Cancer Research Center (FHCRC)
1100 Fairview Ave. N., LE-400
P.O. Box 19024
Seattle, WA 98109-1024 USA

1.6 Study Operations

Study Operations: FHI
P.O. Box 13950
Research Triangle Park, NC 27709 USA

2 INTRODUCTION

2.1 Male Tolerance Studies of Candidate Topical Microbicides

The International Partnership for Microbicides (IPM) is evaluating the antiretroviral drug dapivirine in vaginal gel and vaginal ring formulations for prevention of male-to-female transmission of human immunodeficiency virus (HIV) infection. As part of a comprehensive evaluation of the safety and tolerability of this promising candidate microbicide, IPM has partnered with the Microbicide Trials Network (MTN) to develop and implement a male tolerance study of dapivirine gel.

Male tolerance studies, formerly known as penile irritation studies, play an important role in the clinical trials portfolio of candidate microbicides. This male tolerance study will be carried out to ensure that male partners of the female participants in future trials of dapivirine gel will not be placed at undue risk of genital irritation due to gel exposure. While participants in clinical trials of candidate microbicides are generally counseled extensively regarding known effective means of protection from HIV, correct and consistent condom use cannot be guaranteed in any trial. Thus, in large-scale effectiveness studies, male partners of study participants may knowingly or unknowingly be exposed to candidate microbicides.

Furthermore, considering the research evidence that many women prefer to have their partners' support for microbicide use and that men favor involvement in the decision making process on prevention methods for couples, the assessment of men's acceptability of a microbicide gel is of paramount importance.[1] Phase 1 studies provide a unique opportunity to identify any barriers to consistent use among both target users

and their sexual partners early in the process of product development. Developers can be alerted to the need for changes in product formulation, applicator, or instructions to users before larger and more expensive trials are undertaken.

2.2 Dapivirine Gel

Dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is a substituted di-amino-pyrimidine (DAPY) derivative with potent antiviral activity against HIV-1. Since dapivirine was initially developed as an oral antiretroviral drug, many animal studies were performed using the oral route of administration. Subsequently, to support a microbicide indication, additional preclinical animal studies were performed to evaluate vaginal administration of dapivirine gel formulations.[2]

The preclinical safety studies and clinical trials performed to date support the favorable safety profile and tolerability of dapivirine vaginal gel. The highest daily dose of dapivirine delivered from a vaginal gel to date (approximately 1250 µg/day for 11 days) is 280 times lower than the maximum tolerated single dose for oral dapivirine (350 mg) and more than 600 times lower than the maximum tolerated multiple dose for oral dapivirine (300 mg twice a day for 14 days).

Multiple gel formulations of dapivirine have been developed for vaginal use. Dapivirine Gel 4759 (Gel 4759), is currently being tested in two ongoing IPM trials and is the gel formulation planned for this trial.

2.2.1 Description and Mechanism of Action

Dapivirine is an NNRTI: NNRTIs bind to the HIV reverse transcriptase (RT) enzyme preventing viral replication and therefore production of infectious virus. The primary ingredient of dapivirine gel is water, with hydroxyethylcellulose (HEC) and polycarbophil used as thickening agents. Other ingredients of the gel include methylparaben and propylparaben, as preservatives, propylene glycol as solvent, and sodium hydroxide for pH adjustment. The excipients contained in the drug product formula are United States Pharmacopoeia (USP) grade components (e.g., propylene glycol) with a history of use in currently approved vaginal products.

Table 1: Dapivirine Gel, 0.05% Formulation

Name	Quality Standard	Function	% Composition/Dose (dose = 2.5 g gel)
Dapivirine	Manufacturer's Certificate of Analysis	Active pharmaceutical ingredient (API)	0.05
Purified water	USP	Solvent	90.99
Hydroxyethyl cellulose	NF	Thickening/binding agent	3.50
Polycarbophil	USP	Thickening agent	0.20
Propylene glycol	USP	Solvent	5.00
Methylparaben	National Formulary (NF)	Preservative	0.20
Propylparaben	NF	Preservative	0.05
Sodium hydroxide	NF	pH adjustment	0.01

2.2.2 Strength of Study Product

The dapivirine gel strength proposed for use in MTN-012/IPM 010 is 0.05%.

2.3 Matched Placebo Gel

2.3.1 Description

The matched placebo gel consists of the same ingredients as the corresponding dapivirine gel formulation, but without the active pharmaceutical ingredient (dapivirine).

2.4 Universal Placebo gel

2.4.1 Description

The "Universal Placebo" is a HEC-based gel that was developed for use in clinical evaluations of investigational microbicides. This formulation has been shown to have adequate physical properties, is sufficiently stable as a vaginal gel formulation, and is safe and sufficiently inactive for use in the clinical study of investigational microbicides.[3]

Table 2: Universal Placebo Gel Formulation

Ingredient	Quality Standard	Function	Amount (w/w)
Purified Water	USP	Solvent	96.05
Hydroxyethylcellulose	USP	Tonicity agent	2.7
Sodium Chloride	NF	Preservative	0.85
Sorbic Acid	NF	Thickening/binding agent	0.1
Sodium Hydroxide	NF	pH adjustment	As needed for pH adjusted to 4.4 (± 0.2)

2.4.2 Strength of Study Product

There is no active ingredient in the Universal Placebo gel.

2.5 *In vitro* Studies

2.5.1 *In vitro* Studies of Dapivirine Gel

Anti-HIV-1 Activity

The activity of dapivirine against wild-type (wt) HIV-1, African isolates of HIV-1 (including subtype C virus), and a panel of NNRTI-resistant viruses has been established using *in vitro* models, with 50% effective concentration (EC_{50}) values ranging from 0.3 ng/mL (0.9 nM) against laboratory isolates to <33 ng/mL (<100 nM) for HIV-1 isolates encoding one or more known NNRTI resistance mutations. The anti-HIV activity was also confirmed in an *ex vivo* model of human cervical explant cultures and a humanized severe combined immunodeficient (hu-SCID) mouse model.[4,5]

Resistance

A panel of recombinant viruses was constructed from clinical isolates derived from different geographical origins, representing strains from HIV-1 group M subtypes A, B, C, D, F and H as well as circulating recombinant forms: CRF01_AE, CRF02_AG, CRF05_DF and HIV-1 group O. All group M viruses tested were sensitive to dapivirine with EC_{50} values below 1.0 ng/mL and fold change in EC_{50} values below 4. Susceptibility of virus (V029525) to another NNRTI, delavirdine, was decreased in the absence of known resistance-associated mutations. Although this can be explained by the combination of several polymorphisms, dapivirine was still capable of suppressing this virus strain with an EC_{50} comparable to that of a wt virus (0.6 ng/mL). Eight of the group M viruses carried mutations in the RT coding region at positions associated with NNRTI resistance (positions 98, 101, 106, and 179). The group O virus tested (V029524) naturally harbored amino acids at positions 98 (G), 179 (E) and 181 (C), which are associated with NNRTI resistance in HIV-1 strains from group M. This virus displayed significantly reduced sensitivity to nevirapine (NVP) (89-fold change), delavirdine (140-fold change), efavirenz (EFV) (42-fold change), and dapivirine (150-fold change, which is typical of Type O strains treated with NNRTI).[2]

Cross-resistance

In comparison with NVP, delavirdine (DLV), EFV and emivirine, dapivirine showed significantly better *in vitro* activity against laboratory and recombinant HIV strains resistant to one or more drugs of the same class. The EC_{50} was below 32.9 ng/mL (100 nM) for 80% of the strains, compared with only 56% of the strains for efavirenz.

When tested against 433 clinical isolates with phenotypic resistance to at least one of the NNRTIs NVP, delavirdine, EFV or dapivirine, dapivirine was able to inhibit 46% (202/433) of the samples including 41% (142/350) of the strains resistant to EFV. In contrast, only 10% (24/231) of the dapivirine-resistant strains were inhibited by EFV.[2]

2.5.2 *In vitro* Studies of Matched Placebo Gel

In vitro studies of the matched placebo gel have not been performed.

2.5.3 *In vitro* Studies of Universal Placebo Gel

Anti-HIV-1 Activity

In vitro analyses of anti-HIV activity were performed on Universal Placebo gel following a viral binding assay that consisted of a 2-hour incubation of test compound, HIV-1_{IIIB}, and MT-2 cells. Cell culture followed by further assessments performed after this incubation period showed no significant antiviral or cytotoxic activity. The Universal Placebo gel had negligible effect on virus-induced cytopathic effect at a 1:5 dilution, the highest concentration tested. Additional *in vitro* studies on potential HIV-1 infection of neoplastic T cell lines concluded the Universal Placebo gel had little or no effect on the infection and replication of HIV in human target cells, or the specific replication steps of virus attachment or cell-to-cell fusion.[6]

Cytotoxicity

Dilutions of the Universal Placebo gel in culture medium exhibited negligible toxicity to human vaginal epithelial cells (standard [1-(4,5-dimethylthiazol-2-yl)-3,5 diphenylformazan (MTT)] assay), even at the lowest dilution tested (1:2).[7] Exposure of human vaginal epithelial cells to the Universal Placebo gel resulted in minimal IL-1α induction, even at the lowest dilutions tested (1:2).[3]

Spermatozoa Motility

Analyses of pH (Universal Placebo gel mixed with human seminal plasma, pH 8.03± 0.26) found the HEC formulation did not show significant buffering capacity and could not acidify the alkaline pH of seminal plasma, a favorable result in a placebo formulation.[3] *In vitro* assessments of spermicidal activity utilizing human semen from healthy donors showed the Universal Placebo gel had no significant deleterious effects on sperm motility, even after 60-minute incubation.

2.6 Animal Studies

2.6.1 Animal Studies of Dapivirine Gel

The particular gel formulation planned for this trial has not been tested in preclinical studies; however, it was considered acceptable for use in Phase 1 clinical trials for several reasons. First, all of the ingredients in this formulation of dapivirine gel have been included at the same concentrations in formulations that have been tested in preclinical toxicity studies. Dapivirine gel 4759 differs from Gel 4750 (another formulation of dapivirine gel which will be discussed further below) by a single excipient that is present in a very low level in gel 4750 that is not in 4759. The influence of these ingredients on the toxicity profile of dapivirine has been adequately evaluated previously and has been shown to result in no local or systemic effects.[2] This approach is consistent with the recommendations of Lard-Whiteford et al. (2004) that emphasize the need for vaginal irritation studies only for "formulations that have undergone major modifications."[8] In addition, there has been no evidence of local or systemic toxicity observed in any pre-clinical studies or clinical trials performed with dapivirine via the

intravaginal route. No evidence of toxicity associated with vaginal administration has been observed to date in preclinical studies.

A penile irritation study in rabbits will be conducted prior to initiation of this clinical trial. However, given the absence of notable vaginal findings in pre-clinical studies or clinical trials of similar gel formulations, it is evident that that the investigational product has low irritation potential and is unlikely to cause local toxicity when applied topically to the penis.

Pharmacology

In a series of preclinical safety pharmacology studies, dapivirine was generally devoid of adverse effects on overt behavior, reflexes and other body functions in various animals. Although these studies revealed no cardiovascular effects, there was evidence of an increase in QT interval during the 6-month oral toxicity study in dogs. However, this was only seen at 30 mg/kg/day at which C_{max} and area under the curve (AUC) values were more than 1000 times greater than the values achieved in women following daily use of dapivirine gels 4750 and 4789.

Pharmacokinetics

Systemic exposure to dapivirine was low following vaginal administration of dapivirine gels to rabbits.[2] Much higher systemic exposures were obtained in single-dose oral and subcutaneous toxicity studies in mice and rats, and in repeat dose oral toxicity studies in rats, dogs and monkeys. The free fraction of dapivirine in plasma was 0.19-0.34% in the male rat, 0.18-0.39% in the female rat, 0.21-0.22% in the dog and 0.15% in humans. In rats, tissue to plasma AUC_{0-24} ratios following a single oral dose were 11 in liver, 7-8 in lung, kidney and adrenals, about 4 in spleen and lymph nodes, and 2-3 in brain, heart and muscle. Plasma/tissue equilibrium was rapid, and there was no undue retention of dapivirine in tissues. Following a single oral or vaginal dose of ^{14}C-dapivirine, absorption and distribution of drug-related material to the tissues was moderate in non-pregnant and slow in pregnant female rats. Vaginal dosing did not result in greater distribution to the reproductive tissues (except the vaginal wall) than oral dosing. For virtually all tissues, maximal concentrations after vaginal dosing were <1% of those after oral dosing. Drug-related material was shown to freely cross the placenta to the fetus. In dogs, dapivirine concentrations following oral administration for 14 days were about 9 times higher in liver and muscle, and about 5 times higher in lymph nodes and brain than in plasma. Preliminary metabolism studies demonstrated the presence of free and conjugated metabolites in rats, dogs, monkeys and humans, but the molecular structures have not been elucidated. There was evidence of extensive cytochrome P450 (particularly CYP3A4) mediated metabolism.[2]

Toxicology

General toxicity

No evidence of local or systemic toxicity was observed in a 39-week intravaginal repeat dose toxicity studies in rabbits at nominal concentrations of up to 2 mg/mL. Similarly, no significant findings were observed following intravaginal administration of dapivirine to

rabbits at 5 mg/mL for 13 weeks or up to 20 mg/mL for 14 days. In studies conducted via the oral route of administration, a no observed adverse effect level (NOAEL) was not established in the rat. However, the main findings (effects on liver, thyroid, and pituitary) were considered adaptive rather than adverse responses, and therefore the NOAEL was considered to be 20 mg/kg/day. This dosage was also the NOAEL in the dog. At higher dose levels, hepatotoxicity was observed in dogs and slight hematological and clinical chemistry changes were observed in rats. In the guinea pig, dapivirine (2 mg/mL) did not demonstrate any potential to cause contact sensitization when evaluated using a maximization test.[2]

Mutagenicity

Dapivirine was considered to be non-genotoxic based on the results from a range of *in vitro* and *in vivo* mutagenicity assays, including the Ames Test, L5178Y Mouse Lymphoma Test, Mouse Micronucleus Test, and Unscheduled DNA Synthesis Test.

Reproductive Toxicity

In rats, some effects on the developing fetus were observed following oral administration at maternally toxic doses (80 and 320 mg/kg) of dapivirine. However, there were no effects in rats at the maternally non-toxic dose of 20 mg/kg/day, or in rabbits at up to 90 mg/kg. No toxicity to maternal animals or the developing embryo/fetus was seen in embryo-fetal development studies performed via the vaginal route in rats (up to 3.3 mg/mL using a dose volume of 0.2 mL/kg) and rabbits (up to 2 mg/mL using a dose volume of 1.0 mL).

Effectiveness

Dapivirine blocked vaginal transmission of HIV-1 in a hu-SCID mouse model in which animals received a single vaginal application of dapivirine gel (candidate research gels containing either Carbopol 940 or HEC) prior to a non-invasive vaginal challenge with human peripheral blood lymphocytes (hu-PBL) previously infected *in vitro* with CCR5-tropic and dual tropic (CCR5/CXCR4) HIV-1 strains. Dapivirine prevented a systemic infection with either CCR5 or CCR5/CXCR4 virus strains at concentrations of 2.25 µM (0.7 µg/mL) and higher. The efficacy rate ranged from approximately 70 to 100%, depending on the vaginal gel formulation. The protection resulted directly from the antiretroviral activity of dapivirine, since placebo gels failed to protect and since dapivirine did not show toxicity using mock-infected hu-PBL. Results were better with gels of lower viscosity, probably reflecting the ease with which the vaginal gel was applied to the vagina and thus either the uniformity of distribution over the entire vagina/cervix or the non-traumatic application of the vaginal gel.[5]

2.6.2 Animal Studies of Matched Placebo Gel

The matched placebo formulation planned for this trial has not been tested in preclinical studies; however, all of the ingredients in the gel are approved for use in vaginal products and have been included at the same concentrations in formulations that have been tested in preclinical toxicity studies.[2]

2.6.3 Animal Studies of Universal Placebo gel

Toxicology

Intravenous Administration

Up to 55 intravenous injections of HEC were given to dogs (dose and n not specified) without causing injury other than that typical of the other water-soluble cellulose ethers.[6] 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 the diets containing HEC (n not specified, up to 5%) did not exhibit any adverse effects.[6] 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).

Local Tolerance

A 10-day rabbit vaginal irritation study (10 per arm, 2 arms, placebo gel vs. 0.9% saline control) found the HEC-based placebo gel was not irritating to the vaginal mucosa of rabbits when dosed daily for 10 days.[6, 9] One animal in the HEC-based placebo 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. Histopathologic changes observed were similar to those seen in the control group and likely attributable to those that occur because of the repeated insertion of a catheter, rather than due to any effect of the test samples.

Universal Placebo gel was also used as the placebo comparator in a rectal safety study of a combination microbicide in a macaque model.[10] A third study arm received no product and served as a negative control. Rectal safety of the active product and Universal Placebo 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 Universal Placebo gel. The infrequent evidence of epithelial sloughing and rare incidence of associated blood cells in rectal lavage samples was similar in the Universal Placebo and negative control arm of this study.

Developmental Toxicology

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.[11] While no epidemiological studies of congenital anomalies in infants born to women exposed to HEC during pregnancy have been reported, the Teratogen Information System considers the magnitude of teratogenic risk to a child born after exposure during gestation to be none.

Transmission of SHIV

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).[7] Macaques pretreated with medroxyprogesterone acetate were vaginally administered 1

mL of the HEC gel formulation 15 minutes prior to challenge with 0.5 mL $SHIV_{162p3}$. Investigators monitored total RNA load in the animal plasma for a total of 8 weeks by means of a standard quantitative RT-PCR. The first study utilized the HEC gel formulation at pH 6.5; the second study utilized a formulation at pH 4.4. In both studies, all macaques were infected, as determined by the presence of viral RNA in circulating blood, regardless of the pH of the formulation.

Anti-Herpes Simplex Virus (HSV) Activity

CF-1 mice (n=10 per group) pretreated with medroxyprogesterone acetate (MPA) were administered 0.02 mL of Universal Placebo gel or phosphate-buffered saline (PBS) vaginally, followed by a 0.01 mL of HSV-2 viral inoculum of 10 ID_{50} 0.3 minutes later.[7] On Day 3, vaginal lavage was cultured on human foreskin fibroblasts, and mice were considered infected if a cytopathic effect was observed after 3 days of incubation. Infection rate following pretreatment with Universal Placebo gel (90%) was not significantly different from pretreatment with PBS (80%) or from mice given no treatment (80%). Universal Placebo gel did not enhance susceptibility of mice to HSV-2 when administered 12 hours before vaginal challenge.[7]

Anti-HIV-1 Activity

The effect of the Universal Placebo gel on vaginal transmission of simian human immunodeficiency virus $(SHIV)_{162p3}$ (10^3TCID_{50}) to rhesus monkeys (n=5, n=3, respectively) was determined in two separate studies.[3] Macaques pretreated with MPA were vaginally administered 1 mL of the Universal Placebo 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 reverse transcriptase polymerase chain reaction (RT-PCR). The first study utilized the Universal Placebo gel formulation at pH 6.5; the second study utilized a formulation of pH 4.4. In both studies, all monkeys were infected, as determined by the presence of viral RNA in circulation blood, regardless of the pH of the formulation.[6]

2.7 Clinical Studies

2.7.1 Clinical Studies of Dapivirine Gel

To date, 20 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted: five trials of dapivirine vaginal gel in which 266 participants used dapivirine gel, four trials of dapivirine vaginal rings in which 65 participants used dapivirine rings, and 11 trials of oral dapivirine among 211 participants.[2]

Pharmacokinetics

Dapivirine Gels 4759 and 4789

The particular formulation of dapivirine gel planned for this trial is currently being tested in IPM 020 and IPM 014A.[2] IPM 020 is a double-blind, randomized, placebo-controlled Phase 1/2 expanded safety study involving approximately 180 healthy, sexually active, HIV-negative women to assess the safety of Dapivirine Gel 4759, 0.05% 2.5g and Dapivirine Gel 4789, 0.05% 2.5g as compared to the HEC-based Universal Placebo gel.

IPM 014A is a double-blind, randomized, placebo-controlled Phase 1/2 Study to Evaluate the Safety and Acceptability of Dapivirine Gel 4759, 0.05%, 2.5g, conducted using daily monitored adherence in 320 healthy, HIV-negative women in order to determine whether the gel is safe for daily use by women in Kenya, Malawi, Rwanda, South Africa and Tanzania.

Dapivirine Gel 4750

A similar formulation (Gel 4750) was studied in IPM 012. Gel 4750 included excipient Vitamin E TPGS (dispersing agent, 0.50 %); otherwise the gel formulations (Gel 4750 and Gel 4759) were essentially the same.[2] In IPM 012, the safety and pharmacokinetics of two formulations of dapivirine vaginal gel were compared with the HEC-based Universal Placebo gel in 36 healthy, HIV-negative, sexually abstinent women 18 to 40 years of age. This Phase 1, randomized, double-blind, placebo-controlled trial was conducted at one research center in Belgium. Women were randomized in a 1:1:1 ratio to once daily applications of Gel 4750 (0.05%, 2.5 g), Gel 4789 (0.05%, 2.5 g), or placebo gel for 11 days (Day 1 followed by a 3-day washout period and then for 10 consecutive days, Days 5-14). Dapivirine concentrations were measured in cervicovaginal fluids and plasma on Days 1, 2, 5, 9, 11, 14-17, 19, 21, and 24.

Systemic absorption of dapivirine was low. C_{max} and $AUC_{0\text{-}24h}$ values for dapivirine in plasma were slightly higher for Gel 4750 than Gel 4789 on Days 1 and 14; however, the differences did not achieve statistical significance. For both gels, Day 14 values were 2- to 4-fold higher than values on Day 1. T_{max} was variable; on Day 1 the mean was 23.5 hours for both gels, whereas by Day 14 means were 10-12 hours. Terminal half-life was much longer in plasma (73-90 hours) than in cervicovaginal fluids (15-17 hours).[12]

In summary, the effect of dapivirine on the expression of cytochrome P450 enzymes has been determined in vitro in human hepatocytes, and it was shown that treatment with dapivirine at up to 100 ng/mL did not induce CYP1A2 or CYP3A4/5 activity in cultured human hepatocytes. These data suggest that systemic exposure to dapivirine when used as a microbicide is very unlikely to induce the metabolism of other co-administered medications.

Safety

Dapivirine Vaginal Gels

Dapivirine Gel 001

Dapivirine gel was tested in a 2-part, Phase 1 trial (TMC120-C127) in 48 HIV-negative women and 16 HIV-positive women.[2] Twice-daily application of one of three concentrations of Gel-001 (0.0008%, 0.0016%, or 0.0049%) or a placebo gel was investigated. There were no apparent differences in safety parameters between the three concentrations of Gel-001 and the placebo gel, nor were there apparent safety differences between sexually active and sexually abstinent women. Dapivirine concentrations in plasma remained essentially level in all three dose groups after

maximum concentrations were reached 4 to 8 hours after gel application. The vaginal gels were well-tolerated by healthy participants and HIV-positive participants.

Dapivirine Gel 002

To improve solubility and stability, a new vehicle was developed for vaginal delivery of dapivirine.[2] This new gel was tested in three Phase 1/2 trials: IPM 003, IPM 004 and IPM 005B. In IPM 003, conducted in South Africa, Rwanda, and Tanzania, 112 women used one of three concentrations of dapivirine gel or a placebo gel for 42 days. In IPM 004, a pharmacokinetics trial conducted in South Africa, 18 women used one of three concentrations of dapivirine gel for 10 days. In IPM 005B, conducted in Belgium, 36 women used dapivirine gel (0.02%, 2.65 g) or Universal Placebo gel for 42 days. No treatment related SAEs were observed in these studies. In general, dapivirine gel was well-tolerated with no safety concerns or dropouts due to investigational product-related adverse events (AEs).

Dapivirine Gels 4750 and 4789

The pharmacokinetics of candidates Gel 4750 (the gel formulation most similar to the gel planned for this trial) and Gel 4789 (both 0.05%, 2.5 g) were tested in IPM 012, which was conducted in Belgium in 36 women who applied the vaginal gel once daily for 11 days.[2] There were no SAEs or discontinuations due to treatment-emergent adverse events (TEAEs) in the trial. Most subjects (83-100%) in each group had at least one TEAE during the trial. Headache was the event that occurred most often; 42-67% of subjects in the dapivirine gel groups and 42% of subjects in the placebo gel group reported at least one headache. For most subjects with headaches (13/18; 72%), the event was assessed as possibly related to the investigational product.

All but two TEAEs were assessed as Grade 1 (mild). One subject in the Gel 4789 group had a Grade 2 (moderate) headache assessed as possibly related to the investigational product, and a different subject in the same group had Grade 2 pyrexia assessed as not related to the investigational product. Thirty-four percent (36/105) of TEAEs were assessed as possibly related to the investigational product, and one subject in the Gel 4789 group had two episodes of vulvovaginal pruritus that were assessed as probably related. Among participants using Gel 4750 (the gel formulation most similar to the one planned for this trial), the other TEAEs deemed related to the gel included malaise (1/12) and cervix erythema (1/12).

Of the treatment-emergent adverse events with incidence >5% in the Gel-001, Gel-002, Gel 4750, Gel 4789 dapivirine trials involving HIV-negative participants the following were reported:

Table 3: Treatment-Emergent AEs with Incidence ≥5% in Dapivirine Vaginal Gel Trails

MedDRA Preferred Term	Gel-001, Gel-002, Gel 4750, Gel 4789 N=202
	N (%)
Headache	34 (16.8)
Lower abdominal pain	17 (8.4)
Blood in urine	14 (6.9)
Metrorrhagia	13 (6.4)
Neutropenia	12 (5.9)
Vulvovaginal/genital pruritus	8 (4.0)
Abdominal pain	7 (3.5)
Nasopharyngitis	6 (3.0)
Vaginal/genital discharge	6 (3.0)
Vaginal haemorrhage	6 (3.0)
Abdominal discomfort	5 (2.5)
Nausea	4 (2.0)

Oral Dapivirine

There have been 11 oral administration trials in which a total of 211 participants have been dosed with dapivirine. The maximum tolerated dose established was 350 mg for a single dose, and for multiple doses, 300 mg twice a day for 14 days. There were no deaths during clinical trials of oral dapivirine, and no trials were stopped for safety reasons. A total of 10 participants stopped dapivirine treatment prior to trial completion for safety reasons, six of whom stopped due to a clear dose dependent increase in central nervous system (CNS) and gastrointestinal TEAEs, thereby establishing the maximum tolerated dose at 300 mg twice a day. These TEAEs resolved within 1-2 days after discontinuation of use of oral dapivirine. One of the discontinuations was classified as an SAE, with hospitalization due to elevated liver function tests. This participant was also infected with hepatitis C virus. The only other SAE noted in these trials was a hospitalization due to a bicycle accident.

2.7.2 Clinical Studies of Matched Placebo Gel

Matched placebo gel formulations were studied previously in the IPM studies, TMC120-C127 and IPM 003, as described above.

2.7.3 Clinical Studies of Universal Placebo Gel

Unformulated HEC is known to be a non-irritating substance in humans and skin sensitization is unusual. Doses less than 2 mg/kg by ingestion are not expected to be toxic.[13] No inhalation studies have been conducted, but exposure of humans to the dust in manufacturing operations over many years has not led to any known adverse effects. The placebo gel (HEC) formulation was developed and adopted for use in the HIV Prevention Trials Network (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 randomized, closed label, Phase 1 study of placebo gel (HEC) exposure was conducted in 2003.[14] In this trial, 30 women were randomized to twice-daily vaginal

applications of 3.5 mL of placebo gel (HEC) or polystyrene sulfonate 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. Results of this trial indicated 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 placebo gel reported at least one symptom of mild severity of genital irritation, which included genital burning, soreness and pelvic pain. Three out of 14 women (21.4%) had colposcopic findings that included erythema, petechiae, and peeling. No deep genital disruption was observed in either product group.

A pilot study to optimize trial procedures for Microbicides Development Programme (MDP) 301, a placebo controlled trial of 0.5% PRO 2000 also assessed the acceptability of the placebo gel (HEC).[15] There were no product related SAEs reported.

2.8 Other Clinical Studies of Dapivirine Gel for HIV Prevention

Several other studies of the safety and/or effectiveness of dapivirine for HIV prevention are ongoing or in development. These include studies in the table below.

Table 4: Other Clinical Studies of Vaginal Dapivirine for HIV Prevention

Study Number	Study Description	Phase	Countries	N	Status
IPM 013	Dapivirine vaginal ring PK	1	Belgium	48	Ongoing
IPM 014A	Dapivirine vaginal gel safety	1/2	Kenya, Rwanda, South Africa, Malawi	320	Ongoing
IPM 014B	Dapivirine vaginal gel safety	1/2	South Africa	100	Ongoing
IPM 015	Dapivirine vaginal ring safety	1/2	South Africa, Kenya, Malawi, Rwanda, Tanzania, Zambia	280	Ongoing (South Africa)
IPM 020	Dapivirine vaginal gel safety	1/2	United States	180	Ongoing

2.9 Study Hypotheses and Rationale for Study Design

2.9.1 Study Primary Hypotheses

It is hypothesized that dapivirine gel (0.05%) will be safe and well-tolerated when applied topically to the penis of healthy, HIV-uninfected men, both circumcised and uncircumcised.

2.9.2 Rationale for Study Design

The study design is a standard design for studies of male tolerance of candidate topical microbicides. Similar designs have been utilized for Phase 1 male tolerance studies of topical formulations of UC781, cellulose sulfate, C31G, SPL7013, BufferGel, PRO2000,

and tenofovir. This study involves the inclusion of two placebo arms. The inclusion of both Universal Placebo gel and matched placebo gel arms will help researchers to understand whether any adverse events among participants appear to be associated with excipients in the dapivirine gel formulation, as opposed to dapivirine. Additionally, the inclusion of the Universal Placebo gel arm will provide valuable data regarding male tolerance of this widely used Phase 3 microbicide trial control.

As a secondary study objective, the pharmacokinetic (PK) sampling scheme is designed to identify presence of dapivirine in the blood after penile application sufficient to qualitatively compare relative systemic exposure compared to vaginal dosing, rather than to estimate any PK parameters, which would require a different study design which would be informed by this study. The histologic differences between the glans and the vagina would predict a slower absorption rate constant (ka) and lower bioavailability (F) for the dapivirine applied to the penis which will have the combined effect of lowering C_{max} and delaying T_{max}. The elimination half-life from the blood (and elimination rate constant, k_e) should be the same since these parameters are independent of route of administration, unless there is unlikely mixed order kinetics. Assuming a variety of dosing times for the 7^{th} dose the night prior to the Final Clinic Visit (8 PM through 2 AM) and based on pharmacokinetic simulations using vaginal dosing (absorption rate (k_a) = 0.345, elimination rate (k_e) = 0.0085, T_{max} = 11 hrs), an 8 AM blood collection in clinic the morning following the final dose (~6 to 12 hours after the last dose) will yield anticipated concentrations that bracket the peak concentration (if similar kinetics to vaginal application) or precede it (T_{max} is much longer and k_a lower than vaginal dosing). As such, if blood is collected 24 hours after the final scheduled visit, then the concentration difference from the prior day may not even be detectible as it would be less than 15 to 20% of the value the prior morning, which is near or slightly above assay variation. If the T_{max} is later and k_a lower than with vaginal dosing, there could be no measurable change in peak and trough concentration over a dosing interval and it would require a few days delay to detect and concentration differences. Accordingly, a second blood sample on a later day would add substantially to clinic visits and add little to PK data. Accordingly, we chose to collect only a single blood sample the morning following the final dose. It is also noteworthy, however, that a 7 day dosing plan will not achieve steady-state blood concentrations. Therefore, if systemic absorption is judged to be of potential clinical significance in this study, another study of sufficient duration to achieve steady-state concentrations (approximately 3 weeks) with at least two weeks of blood collections following the last dose would be needed to estimate PK parameters and drug exposure with daily dosing at steady-state.

3 OBJECTIVES

3.1 Primary Objective

- To determine the genitourinary safety of dapivirine gel (0.05%) compared to matched placebo gel and Universal Placebo gel following seven once daily penile applications

3.2 Secondary Objectives

- To assess the pharmacokinetics in plasma following 7 days of once daily penile application of dapivirine gel (0.05%)
- To assess the systemic safety following 7 days of once daily penile application of dapivirine gel (0.05%)
- To assess the acceptability following 7 days of once daily penile application of dapivirine gel (0.05%)

4 STUDY DESIGN

4.1 Identification of Study Design

This is a Phase 1, multi-site, double-blind, randomized, placebo-controlled trial. Participants will be randomized to treatment groups in a 2:1:1 ratio by circumcision status as follows:

Table 5: MTN-012/IPM 010 Study Design

Study Group	Dapivirine Gel (0.05%)	Matched Placebo Gel	Universal Placebo gel	Frequency of Use
Circumcised	12	6	6	Once daily for 7 days
Uncircumcised	12	6	6	Once daily for 7 days

4.2 Summary of Major Endpoints

Primary Endpoints:

- Any evidence of Grade 2 or higher male genitourinary adverse event(s) as defined by the DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009), Addendum 2 (Male Genital Toxicity Table for Use in Topical Microbicide Studies)

Secondary Endpoints:

- Dapivirine concentrations in blood

- Grade 2 and higher clinical and laboratory adverse events as defined by the DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009) and the Male Genital Toxicity Table for Use in Topical Microbicide Studies

- 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 sexual intercourse in the future

4.3 Description of Study Population

The study population consists of healthy, HIV-uninfected, adult males, both circumcised and uncircumcised, who are at least 18 years of age at enrollment and meet the criteria outlined in Section 5.

4.4 Time to Complete Accrual

The time to complete accrual is anticipated to be approximately 8 – 12 weeks.

4.5 Study Groups

The study groups are as follows:

Circumcised
- Dapivirine gel group
- Matched placebo gel group
- Universal Placebo gel group

Uncircumcised
- Dapivirine gel group
- Matched placebo gel group
- Universal Placebo gel group

4.6 Expected Duration of Participation

Once enrolled, a participant undergoes 7 days of study product use, and one additional day of follow-up off study product for a total study duration of approximately 8 days.

4.7 Sites

US study sites selected by the MTN Executive Committee will participate in MTN-012/IPM 010.

5 STUDY POPULATION

5.1 Selection of the Study Population

The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be used to ensure the appropriate selection of study participants. As this is a male tolerance study, only men will be recruited for participation.

5.1.1 Recruitment

Participants will be recruited from a variety of sources across sites, including outpatient clinics, universities and community-based locations. Recruitment materials will be approved by site Institutional Review Boards (IRBs) prior to use.

5.1.2 Retention

Once a participant is enrolled, the study site will make every effort to retain him through follow-up to minimize possible bias associated with loss-to-follow-up. Each study site will establish and follow standard operating procedures for follow-up and retention.

As this is a short-term Phase 1 study, a retention rate of 100% is targeted across sites.

5.2 Inclusion Criteria

Men must meet all of the following criteria to be eligible for inclusion in the study:

1) At least 18 years of age at Screening, verified per site standard operating procedure (SOP)

2) Able and willing to provide written informed consent to be screened for and take part in the study

3) At Screening, able and willing to provide adequate locator information, as defined per site SOP

4) Able and willing to communicate in written and spoken English

5) HIV-uninfected at Screening per Algorithm in Appendix II

6) In general good health, according to the clinical judgment of the Investigator of Record (IoR) or designee

7) Willing to abstain from vaginal, oral and anal intercourse (including receptive anal intercourse), even with a condom; masturbation, and other activities that may cause irritation or injury to the penis during study participation

8) Willing to abstain from using any genitally-applied preparations (except use of usual cleansing products for genital hygiene) other than the study product during study participation

9) Willing to abstain from non-urgent surgical procedures of the penis/GU area for the duration of study participation (e.g. circumcision)

10) At Screening and Enrollment, agrees 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)

5.3 Exclusion Criteria

Men who meet any of the following criteria will be excluded from the study:

1) Participant report of any of the following:
    a. Known adverse reaction to any of the study products or components of the study products (ever)
    b. Post-exposure prophylaxis (PEP) for HIV exposure within 6 months prior to Enrollment
    c. Penile procedures (e.g. biopsy, circumcision) within 42 days or less prior to Enrollment
    d. Participation in any other research study involving drugs, medical devices, or genital products within 30 days or less prior to Enrollment
    e. Within the three months prior to Enrollment, history of a non-gonococcal urethritis and/or sexually transmitted infection (STI), including outbreak of genital herpes or condylomata
    f. For uncircumcised men, the treatment of candidal balanoposthitis/ balanitis within 30 days prior to Enrollment
    g. History of recurrent dermatosis (e.g. eczema)
    h. Non-therapeutic injection drug use in the 12 months prior to Screening
    i. Currently using an immunosuppressant (with the exception of local non-genital use of low potency products e.g. inhaled corticosteroid for asthma)
    j. Has any of the following laboratory abnormalities at Screening:
        i. Hemoglobin < 10.0 g/dL
        ii. Platelet count < 100,000/mm^3
        iii. White blood cell count < 2,000 cells/mm^3
        iv. Alanine transaminase (ALT) and/or aspartate aminotransferase (AST) > 2.5x the site laboratory upper limit of normal (ULN)
        v. Serum creatinine > 1.3x the site laboratory ULN
        vi. Calculated creatinine clearance less than 80 mL/min by the Cockcroft-Gault formula where creatinine clearance in mL/min = (140-age in years) x (weight in kg) x 0.85/72 x serum creatinine in mg/dL

    Note: Otherwise eligible participants with any of the above exclusionary laboratory results may be re-tested. If a participant is re-tested and a non-

exclusionary result is documented within 30 days of providing informed consent for Screening, the participant may be enrolled.

2) At Screening or Enrollment, diagnosed with STI or reproductive tract infection (RTI) requiring treatment, per current Centers for Disease Control and Prevention (CDC) guidelines

3) At Screening or Enrollment, has a clinically apparent Grade 1 or higher genital exam finding (observed by study staff)

4) At Screening or Enrollment, has Grade 1 or higher genital or urinary symptoms

5) At Screening or Enrollment, diagnosed with phimosis or hypospadias

6) At Screening or Enrollment, penile, scrotal piercing or penile tattoos observed during genital examination

7) Has any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

5.4 Co-enrollment Guidelines

As indicated in Section 5.2, participants should not take part in other research studies involving drugs, medical devices, or genital products while taking part in this trial. Participants will be discouraged from taking part in other studies, except for the following:

- Participants may take part in ancillary studies approved by the Protocol Chair

Should any participant report concurrent participation in contraindicated studies after enrolling in this study, the IoR/designee will consult the Protocol Safety Review Team (PSRT) regarding ongoing product use and other potential safety considerations associated with co-enrollment.

6 STUDY PRODUCT

6.1 Regimen

Participants in the circumcised and uncircumcised groups will each be randomized in a 2:1:1 ratio to receive one of three products: dapivirine 0.05% gel, matched placebo gel, or Universal Placebo gel. Participants will apply the contents of one applicator daily for seven days.

Table 6: Study Product Regimen

		Sample Size		
Arm	**Study Product**	**Circumcised**	**Uncircumcised**	**Route and Frequency**
1	Dapivirine gel (0.05%)	12	12	Once daily penile application for 7 days
2	Matched placebo gel	6	6	Once daily penile application for 7 days
3	Universal Placebo gel	6	6	Once daily penile application for 7 days

6.2 Administration

Study staff will instruct participants in the proper method of administration and storage of study gel (dapivirine gel 0.05%, matched placebo gel or Universal Placebo gel). Additional detail on administration and participant education will be provided in the MTN-012/IPM 010 Study Specific Procedures (SSP) Manual.

Study participants will be instructed to apply one dose (the entire contents of one applicator), approximately 2.5 g on to the glans of the penis and then spread to cover the meatus and shaft on Day 0 (Enrollment Visit) and continue daily through Day 6. Additionally, uncircumcised men will be instructed to retract the foreskin, coat the glans and internal foreskin, and replace the foreskin. All participants will be instructed to apply the gel at night before retiring or before the participant's longest period of rest. The gel should remain in place for for 6-10 hours. Participants will also be instructed to return both used and unused applicators at their Final Clinic Visit.

Participants who miss one application of the product will be instructed to complete the missed application on the night following the seventh assigned night, and then to present for their final visit within 24 hours following their last dose. Participants who miss more than one application of the product will be instructed to contact the site for further direction.

6.3 Study Product Formulation

Dapivirine Gel (0.05%)
Dapivirine gel (0.05%) is formulated as a hydrophilic semi-solid (gel) for vaginal administration. The excipients in the drug product formula are pharmacopoeia grade components that have a history of use in currently approved vaginal products. Each pre-filled applicator will contain approximately 2.5 g of dapivirine 0.05% gel.

Dapivirine gel should be stored at 15°C to 30°C (59°F to 86°F).

Matched Placebo Gel
The matched placebo gel consists of the same ingredients as the dapivirine gel formulation, but without the active pharmaceutical ingredient (dapivirine). Each pre-filled applicator will provide 2.5 g of dapivirine matched placebo gel.

Dapivirine matched placebo gel should be stored at 15°C to 30°C (59°F to 86°F).

Universal Placebo Gel

The Universal Placebo gel contains HEC as the gel thickener, purified water, sodium chloride, sorbic acid and sodium hydroxide. 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. HEC, the gelling agent, is used to approximate the viscosity of other microbicide gel candidates. Each pre-filled applicator will contain approximately 2.5 g of Universal Placebo gel.[6]

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

6.4 Study Product Supply and Accountability

6.4.1 Study Product Supply

All products will be supplied (manufactured, filled and wrapped) by IPM (Bethlehem, PA). IPM will manufacture dapivirine 0.05% gel, matched placebo gel and Universal Placebo gel and analyze/release the gels under Good Manufacturing Practices (GMP). Siris Pharmaceutical Services (Bloomsbury, NJ) will label and ship all study products directly to the Pharmacist of Record (PoR) at each study site.

6.4.2 Study Product Accountability

The Pharmacist of Record (PoR) is required to maintain complete records of all study products received from Siris Pharmaceutical Services and subsequently dispensed. All unused study products must be returned to the MTN Director of Pharmacy Affairs after the study is terminated or completed unless otherwise instructed by the MTN Director of Pharmacy Affairs. The procedures to be followed are provided in the MTN-012/IPM 010 Pharmacy Policy and Procedures Manual.

6.5 Study Product Dispensing

Study products will be dispensed only to enrolled study participants, or to study staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. A total of eight individually wrapped pre-filled applicators will be dispensed at the Enrollment Visit (Visit 2). Participants will receive a 7-day supply of product to apply once daily, plus one additional applicator in the event an applicator is rendered unusable (e.g. falls into the toilet). See Section 6.2 for instructions on missed product dose.

6.6 Retrieval of Used/Unused Study Products

Study participants will be instructed to bring all used and unused study products back to the study site at the Final Clinic Visit (Visit 3). All used and unused study products must

be returned to the clinic and documented. The clinic should forward the unused study product to the PoR or designee who will document all unused product returns and store returned study products in a designated area within the site pharmacy.

In the event a participant is permanently discontinued from study product, study product must be retrieved (optimally within 24 hours) and returned to the study site pharmacy.

Study product retrieval will occur either by the participant returning the product to study staff within the specified timeframe or by study staff conducting outreach to retrieve the used and unused product from the participant (e.g., at participant's residence). If the study product(s) are not retrieved within 7 days the MTN-012/IPM 010 PSRT must be informed.

For each participant, used and unused study product remaining in the participant's possession should be retrieved at the Final Clinic Visit. If the participant does not bring his remaining used and unused study product to the Final Clinic Visit, study staff must arrange to retrieve the used and unused study product within 7 business days. If the study product(s) are not retrieved within that timeframe, the MTN-012/IPM 010 PSRT must be informed.

The PoR will document all unused product returns and store returned study products in designated areas within the study pharmacy.

6.7 Study Product Adherence Counseling and Assessment

Study product adherence counseling will be provided to all study participants upon enrollment into the study, to help ensure high rates of study product use. All participants will be counseled to avoid contraindicated penile practices and not to distribute their study products to other people.

Participants will be instructed to apply the product daily before bedtime, usually in the evening or before longest period of rest, which is expected to result in better adherence. To monitor adherence, participants will be asked to use a phone reporting system (PRS) immediately 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 or PTID), and then respond to pre-recorded questions on product use since last call and adherence to protocol guidelines on product use. Responses to the PRS can be entered by either pressing keys (i.e., 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 will then contact the participant to inquire about missed calls (e.g., if the participant forgot to call) and adherence to the study product regimen. Thus, this system allows monitoring

of the reporting on adherence to the PRS on a time-stamped basis. Given that participants are instructed to use the product prior to their longest period of rest and to call the system immediately after applying the product, the calls are a proxy for compliance with time of application. There will be also a recall question on adherence (How many times did you apply the gel on your penis during the days of the trial?) at the Final Clinic/Termination Visit. However, the answer to this question will only be used to replace PRS reporting in the case that PRS data is completely missing. In addition, participants will be asked to return both used and unused applicators and these applicators will be documented by study staff.

6.8 Concomitant Medications

With the exception of genitally-applied preparations (except use of usual genital hygiene cleansing products), concomitant medications will be permitted. Throughout the course of the study, all concomitant medications, including those used to treat AEs, will be recorded on forms designed for that purpose. Prescription medications, over-the-counter preparations, vitamins and nutritional supplements, and herbal preparations will be recorded as concomitant medications.

Prohibited Medications

The following medications are prohibited in MTN-012/IPM 010:

- Immunosuppressive agents, e.g. oral steroids for asthma
- Genitally-applied preparations (except use of usual cleansing products for genital hygiene) other than the study product

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 MTN-012/IPM 010 Study Specific Procedure (SSP) Manual available at www.mtnstopshiv.org.

7.1 Screening

A Screening Visit may take place up to 30 days prior to the Enrollment Visit (Day 0). Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed consent for Screening 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.

Table 7: Screening Visit

Visit 1: Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent for Screening • Assign participant ID (PTID) • Collect locator information • Collect demographic information • Assess eligibility • Reimbursement • Schedule next visit*

Clinical		• Obtain medical history
		• Obtain concomitant medications
		• Perform physical examination
		• Perform genital examination
		• Collect urine
		• Collect blood
		• Provide counseling
		  o HIV pre- and post-test
		  o HIV/STI risk reduction
		  o Abstinence requirements of the study
		• Provide condoms
		• Disclosure of available test results*
		• Refer for RTI/STI treatment *

Laboratory	**Urine**	• Urinalysis (UA) • Gonorrhea (GC)/Chlamydia (CT) by nucleic acid amplification test (NAAT) • Urine culture*
	Blood	• Creatinine, ALT, AST • Complete blood count (CBC) with differential and platelets • HIV-1 testing • Syphilis serology

*if indicated

7.2 Enrollment (Day 0)

Table 8: Enrollment Visit (Day 0)

Visit 2: Enrollment Visit		
Component		**Procedures**
Administrative and Regulatory		• Informed consent for Enrollment and Long-Term Specimen Storage • Review/update locator information • Confirm eligibility • Randomization • Reimbursement • Schedule next visit
Behavioral		• Baseline behavioral questionnaire • Provide instructions on use of Phone Reporting System (PRS) to participants
Clinical		• Review/update medical history • Review/update concomitant medications • Perform physical examination • Perform genital examination • Collect blood • Collect urine* • Provide counseling o HIV/STI risk reduction o Abstinence requirements o Adherence o Product use instructions • Refer for RTI/STI treatment* • Disclosure of available test results*
Laboratory	**Urine**	• Urine culture*
	Blood	• Plasma archive
Study Product Supply		• Provision of 8 pre-filled study product applicators

*if indicated

7.3 Follow-Up Phone Call

Study staff will follow-up with participants via phone call 48-72 hours following the Enrollment Visit. Study staff will inquire about AEs they might have experienced as a result of the study product or procedures performed during the Enrollment Study Visit. If AEs are reported, study staff should follow the guidelines provided in Section 9.0.

Table 9: Follow-Up Phone Call

Follow-up Phone Call	
Component	**Procedures**
Administrative and Regulatory	• Reimbursement~
Clinical	• Record/update AEs

~ Sites to reference SOPs regarding participant reimbursement

7.4 Final Clinic Visit (Day 7) / Termination Visit

The Final Clinic Visit will be targeted to occur within 24 hours of final application.

Table 10: Final Clinic Visit / Termination Visit

Visit 3: Final Clinic Visit / Termination Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Reimbursement • Schedule next visit*
Behavioral		• Product Acceptability and Adherence Questionnaire
Clinical		• Review/update medical history • Review/update concomitant medications • Perform physical examination • Perform genital examination • Collect urine • Collect blood • Collect AEs • Provide counseling o HIV/STI risk reduction o HIV pre- and post-test* • Provide condoms • Disclosure of available test results* • Refer for RTI/STI treatment *
Laboratory	**Urine**	• UA • Urine culture*
	Blood	• Dapivirine level • Creatinine, ALT, AST • CBC with differential and platelets • HIV-1 testing*
Study Product Supply		• Collect all used/unused study product

*if indicated

7.5 Follow-up Procedures for Participants Who Permanently 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.

7.6 Interim 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 (CRF).

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 11: Interim Visit

Interim Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Schedule next visit*

Clinical		• Review/update medical history
		• Review/update concomitant medications
		• Collect urine*
		• Collect blood*
		• Collect AEs
		• Perform physical examination*
		• Perform genital examination*
		• Provide counseling
		  o HIV pre- and post-test*
		  o HIV/STI risk reduction*
		  o Abstinence requirements of the study*
		  o Adherence*
		  o Product use instructions*
		• Provide condoms*
		• Disclosure of available test results*
		• Product use instructions*
		• Refer for RTI/STI treatment *

Laboratory	**Urine**	• Urinalysis (UA)* • Urine culture* • GC/CT by nucleic acid amplification test (NAAT)*
	Blood	• Creatinine, ALT, AST* • Complete blood count (CBC) with differential and platelets* • HIV-1 testing* • Syphilis serology*
Study Product Supply		• Provide study product*

*if indicated

7.7 Clinical Evaluations and Procedures

Physical Examination

- Height (may be omitted after the Screening Visit)
- Weight
- Vital signs
    - Temperature

    - Pulse
    - Blood pressure
- General appearance
- Ear, nose, throat
- Oral mucosa
- Abdomen
- Other components as indicated by participant symptoms

Genital Examination

- General inspection via naked eye and hand-held magnifying glass of the following:
    - Entire penile surface
        - Glans
        - Urethral meatus
        - Internal and external foreskin (if present)
        - Shaft
    - Scrotum
    - Inguinal lymph nodes

7.8 Pharmacokinetics

All participants will have a single time-point PK measurement of dapivirine blood level from blood collected at the Final Clinic Visit (targeted to occur within 24 hours of final application of study product).

7.9 Behavioral Assessments

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

Baseline Behavioral Questionnaire

The baseline behavioral questionnaire is a self-interview that all participants will complete at the Enrollment Visit at a computer terminal located in the site clinic. In addition to demographics, this questionnaire assesses participants' sexual behavior with HIV-negative, positive, or unknown status men and women, and frequency of condom use. The assessment includes questions on past use of sexual lubricants, and questions on alcohol and drug use. It will also assess knowledge about microbicides and anticipated likelihood of product use in the future. This baseline questionnaire allows researchers to contextualize the participants' acceptability attitudes in relation to their sexual history.

Adherence Questionnaire

Adherence will be assessed with the PRS which participants will be asked to call daily. Responses to specific questions on product use since the prior call (e.g., "Did you use the product? Y/N) will constitute one measure of adherence. In addition, at the Final Visit, participants will be asked to report on study product use during the trial via the self-interview.

Product Acceptability Questionnaire

This self-interview will be completed by participants at the Final Clinic Visit. This tool includes structured and semi-structured questions about experiences the participant had using the gel, likes and dislikes concerning the gel, any changes he may have introduced or may wish to introduce in the product used, any problems he may have had or product side-effects (and how much the participant was bothered by them), and likelihood of using a microbicide in the future. It is anticipated that the Product Acceptability Questionnaire will include a few questions similar to those asked on the Baseline Behavioral Assessment so that responses may be compared (i.e. anticipated likelihood of product use).

7.10 Laboratory Evaluations

Local Laboratory

- UA
- Urine culture
- Complete blood count with differential and platelets
- Serum chemistries (creatinine, ALT, AST)
- HIV-1 testing
- Syphilis serology
- Urine GC/CT by NAAT

Network Laboratory (NL)

- Confirmation HIV-1 serology for seroconversion

IPM Designated Laboratory

- Dapivirine level

7.11 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://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/labpolicy.pdf).

MTN-012/IPM 010 Study Specific Procedures Manual (www.mtnstopshiv.org), and site SOPs for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, storage at the site laboratories and shipping information 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.

7.12 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/laboratorypolicy1.pdf).

7.13 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 Regulation CFR 42 Part 72.[16] 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.[17] Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

Site IoRs 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, DAIDS and IPM Medical Safety Physician, Protocol Safety Physician, and SCHARP Clinical Affairs Safety Associate will serve as the PSRT. The MTN SDMC prepares routine AE and clinical data reports (blinded to treatment assignment) for review by the PSRT, which meets via conference call approximately twice per month for the first two months of the study and once per month thereafter or 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 and Safety Review

A multi-tiered safety review process will be followed for the duration of this study. Study site investigators are responsible for the initial evaluation and reporting safety information at the participant level, as well as 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 reviews may be conducted at each of these levels as needed.

MTN SDMC Clinical Affairs staff will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. Adverse event reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer and SDMC Clinical Affairs staff for review.

The PSRT will meet approximately every month via conference call to review clinical data reports generated by the MTN SDMC. The content, format and frequency of the clinical data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to the routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. Experts external to MTN representing expertise in the fields of microbicides, biostatistics, HIV transmission and medical ethics may be invited to join the PSRT safety review. A decision to stop or pause the trial may be made by the PSRT at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

If the protocol team has serious safety concerns, they will request a review of data by the Study Monitoring Committee (SMC). SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Members of the SMC will be independent investigators with no interest (financial or otherwise) in the outcomes of this study. If at any time a decision is made to discontinue enrollment and/or study product use, IPM will notify the FDA and the Clinical Research Site Principal Investigator will notify the responsible IRB expeditiously.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product. 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 study groups, beginning at the time of randomization through the Termination Visit. The term “investigational product” for this study refers to all study gel products.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience, except for possible life-threatening events, for which they are instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where a study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be recorded on study CRFs. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes.

Study staff will record all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product on CRFs. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), Addendum 2 (Male Genital Toxicity Table for Use in Topical Microbicide Studies) http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Addendum_2_Male_Genital_Grading_Table_v1_Nov_2007.pdf. AEs not included in this table will be graded by the DAIDS Table for Grading Adult and Pediatric Events, Version 1.0, December 2004 (Clarification dated August 2009). In cases where a genital AE is covered in both tables, the Male Genital Toxicity Table for Use in Topical Microbicide Studies will be the grading scale utilized.

8.3.2 Serious Adverse Events

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

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

8.3.3 Adverse Event Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. Degrees of relatedness will be categorized according to current DAIDS-approved guidelines in the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, 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 Adverse Event Reporting Requirements

8.4.1 Expedited Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS Expedited Adverse Event Manual, which is available on the Regulatory Support Center (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.nih.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).

8.4.2 Reporting Requirements for this Study

The SAE 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 are required are: dapivirine gel (0.05%), matched placebo gel and Universal Placebo gel.

8.4.3 Grading Severity of Events

The grading of severity of events and the reporting period will be the same as for all AEs, as described in Section 8.3.1. The most current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) will be used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

8.4.4 Expedited AE Reporting Period

The expedited AE reporting period for this study begins once the participant is randomized and continues through the participant's termination from the study.

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 Regulatory Requirements

Information on all reported AEs will be included in reports to the U.S. Food and Drug Administration (FDA) and other applicable government and regulatory authorities. Site IoRs/designees will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. Site IoRs/designees also will submit AE information and any other relevant safety information to their IRBs in accordance with IRB requirements.

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. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to responsible site IRBs according to their individual requirements.

9 CLINICAL MANAGEMENT

Guidelines for clinical management and permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to permanently discontinue study product at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. The IoR/designee will document permanent discontinuations on applicable CRFs.

9.1 Grading System

The primary grading system is located in the Male Genital Toxicity Table for Use in Topical Microbicide Studies, which is labeled as Addendum 2 in the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events (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 General Criteria for Permanent Discontinuation of Study Product

Given the short follow-up period of study product exposure in MTN-012/IPM 010, participants are not anticipated to be temporarily held from study product for any reason; therefore criteria for temporary hold are not included within this protocol.

A participant will be permanently discontinued from product use by the IoR/designee for any of the following reasons:

- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use according to the judgment of the IoR/designee

- Participant reports the use of PEP for possible HIV-1 exposure

9.4 Permanent Discontinuation in Response to Observed Adverse Events

Grade 1
Participants who develop a Grade 1 AE that is not specifically addressed below may continue use of study product per protocol.

Grade 2
Participants who develop a Grade 2 AE or toxicity judged to be related to study product should have the study product permanently discontinued.

Grade 3 or 4
Participants who develop a Grade 3 or higher AE or toxicity regardless of relatedness to study product should have the study product permanently discontinued.

9.5 Management of Specific Toxicities

Product related genital findings of definite erythema, edema, ecchymoses, vesicle/bulla, pustule, abrasion, ulceration or laceration and other findings at the discretion of the investigator should be examined every 48 to 72 hours until resolved.

9.6 Genital Sexually Transmitted Infection/ Reproductive Tract Infection

The IoR/designee should manage STI/RTI per current CDC guidelines, available at http://www.cdc.gov/std/treatment/. Observed single oral dose should be provided whenever possible.

9.7 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The Site IoR 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 PSRT. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the Office of Human Research Protections (OHRP)), 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.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is a Phase 1, double-blind, randomized, controlled comparison of 7 days of once daily exposure to dapivirine gel (0.05%), matched placebo gel or Universal Placebo gel, and follow-up among HIV-uninfected, circumcised and uncircumcised men.

10.2 Study Endpoints

Primary endpoints
Consistent with the primary study objective to assess the safety of study drug when administered once daily for 7 days on the penis, the following primary endpoints will be assessed:

- Any evidence of Grade 2 or higher male genitourinary AEs as defined by the DAIDS AE Table, Addendum 2 (Male Genital Toxicity Table for Use in Topical Microbicide Studies)

Secondary endpoints
Consistent with the secondary study objectives to assess the acceptability of, a short-term regimen of dapivirine, and to assess the effect of this regimen on the penis, the following endpoints will be assessed:

- Dapivirine concentrations in blood

- Grade 2 or higher clinical and laboratory adverse events as defined by the DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated August 2009) and the Male Genital Toxicity Table for Use in Topical Microbicide Studies

- 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 sexual intercourse in the future

10.3 Primary Study Hypotheses

MTN-012 hypothesizes that dapivirine gel (0.05%) will be safe and well-tolerated for once daily topical use for 7 days among healthy uncircumcised and circumcised men.

10.4 Sample Size and Power Calculations

The primary aim of the study is to assess the safety of penile application of dapivirine gel versus two placebo gels among HIV uninfected circumcised and uncircumcised men. The proposed total sample size is approximately n=48 participants with approximately 24 circumcised men and 24 uncircumcised men. Stratifying by

circumcision status, there will be 12 men in the dapivirine group and 6 participants in each placebo group. This sample size is based upon the size of similar Phase 1 studies of topical microbicide products.

As a means to characterize the statistical properties of this study, the following table presents the probability of observing zero, at least one, and two or more safety endpoints among the maximum sample size of 24 men (circumcised and uncircumcised combined) using dapivirine for various "true" event rates:

Table 12: Analysis of AE Frequency (n=24)

Event Rate	P (0 events | n=24)	P (≥1 event | n=24)	P (≥2 events | n=24)
1%	79.6	21.4	2.4
5%	29.2	70.8	33.9
10%	8.0	92.0	70.8
15%	2.0	98.0	89.4
25%	.10	>99.9	99.1
35%	<.001	>99.9	>99.9
45%	<.001	>99.9	>99.9

For example, if the true rate of a given endpoint is five percent, the probability that the endpoint will be observed in at least one of the (minimum of) 24 men exposed to dapivirine is 70.8%.

The actual number of men using dapivirine who will be available for analysis is likely to be approximately 12 in each individual group of circumcised and uncircumcised men. Given this, the table below presents the probability of observing zero, at least one, and two or more safety endpoints assuming 6 men were randomized to each placebo gel for various "true" event rates:

Table 13: Analysis of AE Frequency (n=12)

Event Rate	P (0 events | n=12)	P (≥1 event | n=12)	P (≥2 events | n=12)
1%	88.6	11.4	0.62
5%	54.0	46.0	11.8
10%	28.2	72.0	34.0
15%	14.2	85.8	55.7
25%	3.2	96.8	84.2
35%	0.67	99.4	95.8
45%	0.07	99.9	99.2

The actual number of men in either placebo group who will be available for analysis is likely to be approximately 6 in each group. Given this, the table below presents the probability of observing zero, at least one, and two or more safety endpoints assuming 6 men were randomized to each placebo gel for various "true" event rates:

Table 14: Analysis of AE Frequency (n=6)

Event Rate	P (0 events | n=6)	P (≥1 event | n=6)	P (≥2 events | n=6)
1%	94.1	5.9	.15
5%	73.5	26.5	3.3
10%	53.1	46.9	11.4
15%	37.7	62.3	22.3
25%	17.8	82.2	46.6
35%	7.5	92.5	98.1
45%	2.8	97.2	83.6

An alternative way of describing the statistical properties of the study design is in terms of the 95% confidence interval for the true rate based on the observed data. The table below shows the exact 2-sided 95% confidence intervals for the probability of an event based on a particular observed rate. If none of the 12 participants receiving a treatment regimen experience a safety event, the 95% exact 2-sided upper confidence bound for the true rate of such events in the treatment population is 26.4%.

Table 15: Exact 2-sided 95% Confidence Intervals Based on Observing a Particular Rate of Safety Endpoints for Arms of Size 6 and 12

Observed Event Rate	Confidence Interval (%)
0/6	0, 46.9
1/6	.4, 64.1
2/6	4.3, 77.7
0/12	0, 26.4
1/12	.21, 38.4
2/12	2.1, 48.4
0/24	0, 14.2
1/24	.11, 21.1
2/24	1.0, 27.0

10.5 Participant Accrual, Follow-up and Retention

Each enrolled participant will be followed for approximately 1 week. Participants will return for a final follow-up visit targeted to occur 24 hours after the final application of gel. Given that enrollment will be completed in approximately 12 weeks the last follow-up visit should occur approximately 13 weeks after study initiation.

Participants lost to follow-up and/or participants who permanently discontinue product will not be replaced. However, every effort will be made to complete their regularly scheduled safety evaluations. Each site will target retention of 100%.

10.6 Randomization

Men will be randomized at a 2:1:1 ratio to one of the three treatment arms. Randomization will be stratified by site and circumcision status to ensure balanced assignment to each product (dapivirine, matched placebo, or Universal Placebo gel).

The randomization scheme will be generated and maintained by the SDMC. The SDMC will provide each study site with two sets of randomization envelopes (for circumcised and uncircumcised) to be stored and used in the study clinic. Clinic staff will assign these envelopes in sequential order, by envelope number, to eligible participants.

Assignment of the randomization envelope is considered the effective act of participant enrollment/randomization. Clinic staff will prepare a written prescription contained within the envelope that, among other things, documents the randomization envelope number and randomization code indicating the product (dapivirine, matched placebo, or Universal Placebo gel) to which the participant was assigned. Multiple codes will be utilized to conceal and protect the randomization assignments in this study. Clinic staff will store assigned randomization envelopes and copies of the study prescription in participants' study charts.

10.7 Blinding

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

10.8 Maintenance of Trial Randomization Codes

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

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

10.9 Data and Safety Monitoring and Analysis

10.9.1 Study Monitoring Committee

No Data and Safety Monitoring Board oversight is planned for this study. The MTN SMC will conduct a review of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, study or lab issues, and, in a closed report, safety data by arm of the study. This review will take

place at least once during the study period, and as needed. At the time of review, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

10.9.2 Data Analysis

For analyses comparing dapivirine gel (0.05%) to the matched placebo gel, data from approximately 18 males will be included (12 participants in the dapivirine arm and 6 in the matched placebo arm) for the uncircumcised and circumcised male participant separately, and for analyses comparing dapivirine gel to the Universal Placebo gel, data from approximately 18 men will be included (12 participants in the dapivirine arm and 6 participants in the Universal Placebo gel arm) for the uncircumcised and circumcised males separately. The circumcised and uncircumcised male participants may be combined which would result in 24 men in the dapivirine arm, 12 participants in the matched placebo gel arm, and 12 participants in the Universal Placebo gel arm. The same comparisons will be made between dapivirine gel (0.05%) and each of the placebo arms.

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

To assess the adequacy of the randomization, participants in the dapivirine gel, matched placebo gel, and Universal Gel arms will be compared for baseline characteristics including demographics and laboratory measurements using descriptive statistics. Due to the small sample size, formal comparisons will not be done.

Primary Analyses

The primary aim of the study is to assess the genitourinary safety of dapivirine gel (.05%) following seven daily penile applications. All visits in which a man has been exposed to the study product will be included in the primary analysis of safety. Secondary intent-to-treat analyses may also be performed. To assess genitourinary safety, the number and the percentages of participants experiencing at least one Grade 2 or higher male genitourinary AE will be tabulated by study arm using MedDRA preferred terms. Each participant will contribute once in each category (i.e. only for highest severity AE for each participant) for the calculation of event rates. The number and percentage of participants experiencing each type of genitourinary AE (including

AEs leading to study discontinuation) will be tabulated by severity and relationship to treatment for each treatment group. Overall summaries by treatment group include the number and percentage of participants experiencing: (1) any experience; (2) any moderate, severe, or life-threatening experience. Genitourinary AEs that lead to study product discontinuation will be listed in a separate data listing.

Secondary Analyses

Pharmacokinetics

The percent of participants with dapivirine concentrations in blood will be estimated. These values will be compared to similar data from vaginal dosing studies. Dapivirine concentrations will be plotted versus hours post dosing time for all participants, by circumcision group, to explore temporal trends among the participants. Based on the argument provided in the rationale, measured dapivirine values are estimated to be within 20% of peak concentrations which will be sufficient to identify the relative absorption from vaginal compared to the penile route. Population-based PK methods can be used to explore PK parameters, but the sample size will be too small to predict likely success. However, this is not an objective of the study.

Systemic Safety

To assess the systemic safety following 7 days of once daily penile application of dapivirine gel (0.05%), the number and the percentages of participants experiencing at least one Grade 2 or higher clinical and laboratory AE will be tabulated by study arm. AEs will be tabulated using MedDRA preferred terms. Each participant will contribute once in each category (i.e. only for highest severity AE for each participant) for the calculation of event rates. The number and percentage of participants experiencing each type of Grade 2 or higher clinical and laboratory AE will be tabulated by severity and relationship to treatment for each treatment group. Overall summaries by treatment group include the number and percentage of participants experiencing: (1) any experience; (2) any moderate, severe, or life-threatening experience. Systemic AEs that lead to study product discontinuation will be listed in a separate data listing.

Acceptability

One secondary study objective is to evaluate aspects of product acceptability. To evaluate acceptability, the proportion of participants who at their Final Clinic Visit report via acceptability questionnaire that they would be very likely to use the candidate microbicide during sexual intercourse in the future will be calculated by treatment arm.
We will compare acceptability of study products using a 10-point Likert scale, as well as the proportion of participants who report high intentionality, operationalized as having a rating in the upper one third of the 10-point Likert scale.

10.9.3 Missing Data

We are targeting a retention rate of 100% over the 7- 8 day follow-up period. If missing data rates are higher than anticipated (over 10%), robust methods such as nonparametric tests and GEE using all available baseline predictors of the missing

outcomes as covariates will be used to obtain less biased estimates of the treatment effect.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team and the representative of the Behavioral Research Working Group (BRWG). 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 CRFs to be used as source documents. Non-Audio Computer Assisted Self Interview (CASI) data are transferred to the MTN SDMC.

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/research/resources/DAIDSClinRsrch/)

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, for each of the three investigational products tested, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval for Dapivirine gel 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 (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 DAIDS. No study records may be moved to an off-site location or destroyed prior to receiving approval from DAIDS.

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites (http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/qmppolicy.pdf).

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by Pharmaceutical Product Development, Inc. (PPD) (Wilmington, NC) in accordance with current DAIDS policies. 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 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

The IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. The IoR/designee also will allow inspection of all study-related documentation and observation of study procedures by authorized representatives of the FDA, MTN Coordinating and Operations Center (CORE), SDMC, IPM, NL, NIAID, OHRP and local and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR will have obtained IRB approval and the protocol will have been submitted to the FDA. The IoR will permit audits by the NIH, OHRP, IPM, FDA, MTN Core, IRBs/ECs or any of their appointed agents.

13.1 Institutional Review Boards/Ethics Committees

Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent forms (ICF), and study-related documents (such as participation education and recruitment materials) are reviewed by the IRB/EC responsible for oversight of research conducted at the study sites. Any amendments to the protocol must be approved by the responsible IRBs prior to implementation.

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 forms approved, as appropriate, by their local IRB/EC and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific 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 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 Study Coordination

IPM holds the Investigational New Drug (IND) application for this study, and is responsible for all communication and submissions to the FDA regarding the IND. IPM will provide DAIDS with copies of all regulatory documents submitted to the IND to support cross-referencing with other applications for the investigational products. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement (CTA) executed by DAIDS and IPM.

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 study 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 SMC.

13.4 Risk Benefit Statement

13.4.1 Risks

Phlebotomy may lead to excessive bleeding, discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Genital examination may cause participants to feel mild pressure, discomfort and/or embarrassment. Disclosure of HIV and STI status may cause worry, sadness or depression. 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.

Participants in sites requiring partner notification in response to diagnosed STI 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.

Based on adverse events reported among female participants in previous studies, male exposure to study gel may be associated with:

- Headache
- Lower abdominal pain
- Blood in urine
- Neutropenia
- Abdominal pain
- Nasopharyngitis
- Abdominal discomfort
- Nausea

13.4.2 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 opportunity to contribute to the field of HIV prevention research.

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical examination, genital examination, and routine laboratory testing related to blood, liver, and kidney function. Participants will be referred for STI treatment in accordance with CDC guidelines and referred to STI testing and treatment for their partners. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals.

13.5 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 IoR 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 current DAIDS policies. 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.

In addition to informed consent forms, the Protocol Team will work with study staff and community representatives to develop locally-appropriate materials about the study and a standardized approach to the informed consent process to be implemented at all study sites, which will be detailed in the study-specific procedures manual.

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 importance to this study:

- The unknown safety and unproven efficacy of the study products
- The importance of participants in all six 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

13.6 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 areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers to 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 the following:

- NIH and/or its contractors, including study monitors
- Representatives of IPM
- Representatives of the MTN CORE, SDMC, and/or NL
- The US FDA, OHRP, and/or other government and regulatory authorities
- Site IRBs/ECs

The MTN has obtained a Certificate of Confidentiality from the US Department of Health and Human Services (HHS) that will be applicable for this study. This Certificate protects study staff from being compelled to disclose study-related information by any US Federal, State or local civil, criminal, administrative, legislative or other proceedings. It thus serves to protect the identity and privacy of study participants.

13.7 Special Populations

13.7.1 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.

13.8 Compensation

Pending IRB approval, participants will be compensated for time and effort.

13.9 Communicable Disease Reporting

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

13.10 Access to HIV-related Care

13.10.1 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. In accordance with the policies of the NIH, participants must receive their HIV test results to take part in this study.

13.11 Study Discontinuation

This study may be discontinued at any time by NIAID, the MTN, IPM, the US FDA, the OHRP, other government or regulatory authorities, or site IRBs/ECs.

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies and a CTA between IPM 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, NIMH, and IPM for review prior to submission.

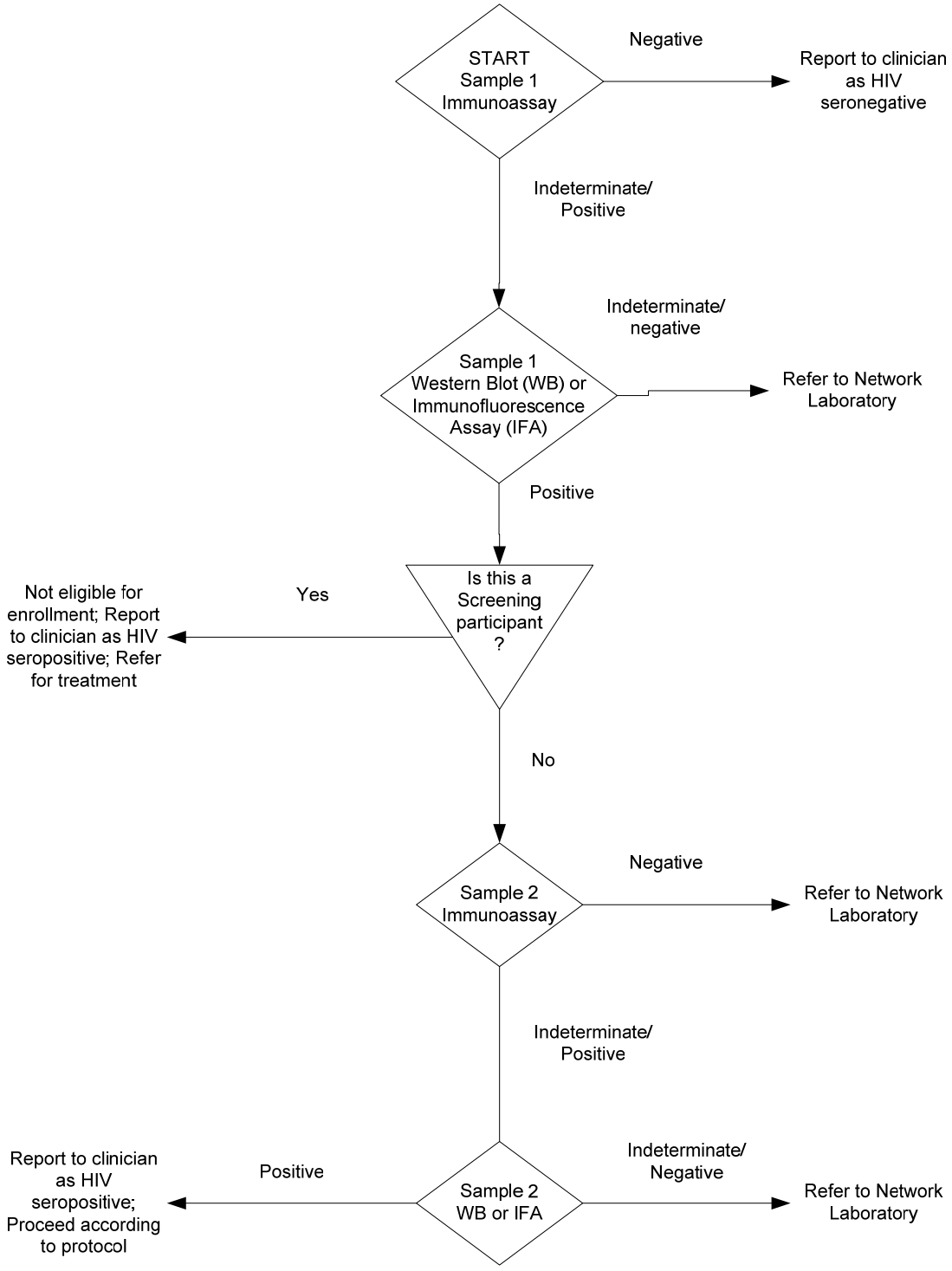
15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

		SCR	ENR	PHONE CALL	FINAL CLINIC	INTERIM
ADMINISTRATIVE & REGULATORY						
Informed consent		X	X			
Assignment of PTID		X				
Locator information		X	X		X	X
Demographic information		X				
Eligibility assessment		X				
Eligibility confirmation			X			
Randomization			X			
Reimbursement		X	X	X	X	
Schedule next visit		*	X		*	*
BEHAVIORAL ASSESSMENTS						
Baseline Behavioral Questionnaire			X			
Instructions on use of Phone Reporting System			X			
Product Acceptability and Adherence Questionnaire					X	
CLINICAL						
Collect/update medical history		X	X		X	X
Collect/update concomitant medications		X	X		X	X
Physical examination		X	X		X	*
Genital examination		X	X		X	*
Collect urine		X	*		X	*
Collect blood		X	X		X	*
HIV/STI risk reduction counseling		X	X		X	*
HIV pre and post-test counseling		X			*	*
Abstinence requirements/counseling		X	X			*
Adherence counseling			X			*
Provision of condoms		X			X	*
Product use instructions			X			*
Disclosure of available test results		*	*		*	*
Collect AEs				X	X	X
Refer for RTI/STI treatment		*	*		*	*
LABORATORY						
Urine	Urine GC/CT NAAT	X				*
	Urinalysis	X			X	*
	Urine culture	*	*		*	*
Blood	CBC with differential and platelets	X			X	*
	HIV-1 testing	X			*	*
	Serum chemistries (Cr, AST/ALT)	X			X	*
	PK				X	
	Syphilis serology	X				*
	Plasma archive		X			
STUDY PRODUCT						
Provision of study product			X			*
Collect used/unused study product					X	

X = Required, * = As Indicated

APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING FOR SCREENING AND ENROLLED PARTICIPANTS



APPENDIX III: SAMPLE INFORMED CONSENT FORM (SCREENING)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-012/IPM 010

Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

November 29, 2010

PRINCIPAL INVESTIGATOR: [INSERT NUMBER]
PHONE: [INSERT NUMBER]
Short Title for the Study: Male Tolerance of Dapivirine Gel

INTRODUCTION

You are being asked to take part in the screening exams and tests for this research study because you are a male and at least 18 years old. Approximately 48 men will take part in this study across multiple sites. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH) and the International Partnership for Microbicides (IPM). The person in charge of the study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Three products are in this study, dapivirine gel (0.05%) and two gels without any drug; a matched placebo gel and Universal Placebo gel. These gels are supplied by IPM. The screening includes interview questions, urine and blood tests, a physical exam, and an examination of your penis.

YOUR PARTICIPATION IS VOLUNTARY

This consent form provides information about the screening tests that will be discussed with you. Study staff will talk with you about this information. You are encouraged to ask questions about the screening visit at any time. 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 given a copy of the signed 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 any time
- 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 learned 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?
The purpose of this study is to find out whether dapivirine gel (0.05%) causes irritation to the penis when used once a day for seven days and whether or not the amount of irritation is similar to that caused by the matched placebo gel or Universal Placebo gel. To be in this study you must agree not to have sexual intercourse (vaginal, anal, or oral sex) and also agree not to masturbate and to avoid any activity that may cause irritation or injury to your penis for the duration of gel use during the study (approximately 7 days).

If you are selected, you will be one of about 48 men evaluated (24 circumcised and 24 uncircumcised) at multiple sites located in the United States [SITES TO INSERT]. About 24 men will receive dapivirine gel (0.05%), 12 men will receive matched placebo gel, and 12 men will receive the Universal Placebo gel. You will be randomly assigned (like the flip of a coin) to receive either dapivirine gel (0.05%), matched placebo gel or the Universal Placebo gel. You will have a 1 in 2 chance of receiving dapivirine gel (0.05%). Neither you nor the research staff will know which of the products you have received. If you are enrolled, your participation in this study will last about a week and you will have three clinic visits, including today's visit.

HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS. Dapivirine gel is *experimental* for HIV prevention which means that this gel has not been approved for application on either male or female genitals. This means **we do not know if it works to protect against HIV.** In future studies, researchers would like to see if dapivirine gel, when inserted into the vagina or rectum, can prevent the transmission of HIV. In order to do that, researchers need to make sure dapivirine gel is safe for men and understand how men feel about using the gel.

WHAT DO I HAVE TO DO IF I TAKE PART IN SCREENING?
The screening visit will take about [SITES TO INSERT] hours to be completed today. 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 medical history, and any medicines you are taking and how we can contact you
- Have a physical exam
- Have a genital exam
- Learn about:
    - how to avoid infections passed during sex
    - the meaning of your test results, including your HIV test results
    - if you test positive for HIV, this study will not provide you with treatment, but study staff will provide you with immediate counseling and also refer

you to available sources of medical care, counseling, and other services you may need

- How to follow the rules of the study (including avoiding masturbation and oral, anal, vaginal sex while using study product even with a condom for approximately 7 days)
- Provide a urine sample to check for urinary tract infection, gonorrhea, and Chlamydia
- Have a blood sample [AMOUNT NOT TO EXCEED XX ML] taken to check the following:
  - the health of your blood, liver and kidneys
  - HIV status
  - syphilis status
- 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
- You will also receive condoms as condoms have been found to greatly reduce the spread of sexually transmitted diseases. You may use these condoms until you begin using the study gel, at which point you will need to avoid all sexual activity as per the guidelines of this study

WHY WOULD THE DOCTOR STOP THE SCREENING PROCEDURES EARLY?

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

- The study is cancelled by the US Food and Drug Administration (FDA), US National Institutes of Health (NIH), the MTN, IPM, the Office for Human Research Protections (OHRP), the other government or regulatory agencies, or the Institutional Review Board (IRB)/Ethics Committee (EC). 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
- Any other reasons that may prevent you from completing the study

Data collected about you up to the time of withdrawal will remain in the trial database and be included in the data analysis.

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 when your blood is drawn

- You may have more than expected bleeding, a bruise, swelling, or infection where the needle goes into your arm

Risk of Genital Exams:

- You may feel discomfort, pressure or embarrassment when your genitals are examined

Other Possible Risks:

- You may become embarrassed, worried, or nervous when discussing personal questions about 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
- Learning you have HIV or other infections could worry you or make you nervous. Finding out your HIV status could also cause problems between you and your partner. 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 others may learn that you are taking part in the study here.

[SITES TO INSERT IF APPLICABLE: It's possible others may learn of your involvement in this research study and treat you unfairly as a result. If you become aware of this please let study staff know and they can provide you with information regarding how to handle situations such as these.]

[SITES TO INSERT IF APPLICABLE: site specific required risks here, including unknown risks.]

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You may not get any direct benefit from the screening exams and tests. However, you may benefit from the following:

- Physical exam and genital exam
- Tests for sexually transmitted infections and HIV (which may detect infections without obvious symptoms). If you have any of these infections, you will be counseled and referred for treatment. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. You can also bring your partner here for counseling and referral for testing and treatment for STIs if this is needed
- Tests to check your general health and the health of your liver, kidneys, and blood
- Counseling regarding safe sex

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. Regardless of your decision to participate in MTN-012/IPM 010, neither your care nor your relationship will change with [INSERT INSTITUTION NAME] in any way.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information private. Your physical and genital 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.

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 learns 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.

Your records may be reviewed by:

- US FDA
- US NIH or their designee
- OHRP
- [INSERT NAME OF SITE] IRB/EC
- Study staff
- Study monitors
- IPM

[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 [LOCAL 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 [LOCAL HEALTH AUTHORITY].

WHAT ARE THE COSTS TO ME?

There are no costs to you or your health insurance provider for the study procedures and exams.

WILL I RECEIVE ANY PAYMENT?

You will be compensated for your time and effort for the screening visit. You will receive [SITE 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 INCLUDE/AMEND THE FOLLOWING IF APPLICABLE*:*]

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 at any time. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled.

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.

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 TO INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF THE ABOVE]

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

- [SITE TO INSERT NAME OR TITLE OF THE 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 THE 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 IV: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT & STORAGE AND FUTURE TESTING OF SPECIMENS)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-012/IPM 010

Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

November 29, 2010

PRINCIPAL INVESTIGATOR: [INSERT NAME]
PHONE: [INSERT NUMBER]
Short Title for the Study: Male Tolerance of Dapivirine Gel

INFORMED CONSENT
You are being asked to volunteer for a research study known as MTN-012/IPM 010.

INTRODUCTION
You are being asked to take part in this research study because you a male and at least 18 years old at the Screening Visit, and have passed the screening requirements for this research study. Approximately 48 men will take part in this study across multiple sites. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH) and the International Partnership for Microbicides (IPM). The person in charge of the study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Three products are in this study, dapivirine gel (0.05%) and two gels without any drug; a matched placebo gel and Universal Placebo gel. These gels are supplied by IPM.

YOUR PARTICIPATION IS VOLUNTARY
This is an enrollment consent form that gives you information about the study. This study also asks for your permission to store leftover samples for future testing. 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 given a copy of the signed form to keep.

Before you learn about this study, it is important you know the following:
- If you do not want to, you do not have to join this study
- You may decide not to have the study procedures or you may withdraw from the study at anytime
- Some people may not be able to join the research study because of information found out 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?

The purpose of this study is to find out whether dapivirine gel (0.05%), when used once a day for seven days, causes irritation to the penis and whether or not the amount of irritation is similar to that caused by the matched placebo gel or Universal Placebo gel. Your selection as a participant is based upon your qualifications. To be in this study you must agree not to have sexual intercourse (vaginal, anal, or oral sex, even with a condom) and also agree not to masturbate and to avoid any activity that may cause irritation or injury to your penis for the duration of gel use during the study (approximately 7 days).

HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS. Dapivirine gel is *experimental* for HIV prevention which means that this gel has not been approved for application on either male or female genitals. This means **we do not know if it works to protect against HIV.** In future studies, researchers would like to see if dapivirine gel, when inserted into the vagina or rectum, can prevent the transmission of HIV. In order to do that, researchers need to make sure dapivirine gel is safe for men and understand how men feel about using the gel.

STUDY GROUPS

If you decide to take part in the study, you will be placed in one of the three groups and each study gel group will contain both circumcised and uncircumcised males who receive either dapivirine gel (0.05%), matched placebo gel, or Universal Placebo gel. About 24 men will receive dapivirine gel (0.05%), 12 men will receive matched placebo gel, and 12 men will receive the Universal Placebo gel. Your group will be chosen by random (for example, like flipping a coin or throwing dice). You cannot choose your group nor can the study staff 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. Before the study ends, you will not be told which product you received nor should it be medically necessary to inform you of which product you received. All three groups are 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 Enrollment 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 you will:

- Answer questions to make sure you are still eligible to join this study
- 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 history
- Tell us if there have been changes to any medicines you are taking

Learn about:

    - how to avoid infections passed during sex
    - abstinence requirements of this study; including avoiding masturbation and oral, anal, vaginal sex even with a condom while using study product; approximately 7 days
- Have a blood sample taken [AMOUNT NOT TO EXCEED XX ML] in case there is a question about your lab results.
- You may provide a urine sample to check for urinary tract infection, gonorrhea, and Chlamydia
- Have a physical exam
- Have a genital exam
- Answer questions about your behavior, including questions about your sexual activity in the past three months, condom use, sexual lubricant use, and questions about your alcohol and drug use.
- Receive instructions about how to call an automated phone system each time you use the gel at home. 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.
- Be referred for treatment of reproductive tract infections and/or sexually transmitted infections, if you need them.
- Receive a 7-day supply of the study product plus one extra in case one gets damaged (e.g. falls in the toilet)
- Receive instruction on when and how to use the study product. Also discuss with study staff the importance of using the gel daily.
- Schedule your next visit
- Receive test results, if you have not already received them

During the Follow-up Phone Call (which occurs 48-72 hours after your visit today) you will:

- Tell study staff if you had any health problems or other problems having to do with the study since your last visit

<u>We will also ask you to do the following at your final clinic visit:</u>

- 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 history
- Tell us if there have been changes to any medicines you are taking
- Tell us about any physical problems you may have been having
- Have a physical exam
- Have a genital exam
- Learn how to prevent infections passed during sex
- Be referred for treatment of reproductive tract infections and/or sexually transmitted infections, if you need them
- You may provide a urine sample to check for urinary tract infection, gonorrhea, and Chlamydia

- Blood will be taken to [AMOUNT NOT TO EXCEED XX ML]:
    - Check the health of your blood, liver, and kidneys
    - Check how much of the study drug is present in your body
- Answers questions about your experience using the study gel, including what you did not like about the gel and how often you used it
- Return used/unused study product (including the one 'extra' gel, if you did not need to use it)
- Receive condoms from study staff
- Receive test results, if you have not already received them

It may be necessary to check your HIV status at your final clinic visit. This blood test will be performed only if you or if a study clinician thinks you need to be tested.

- If you are tested for HIV, study staff will discuss the meaning of your test results
- If you test positive for HIV, this study will not provide you with treatment, but study staff will provide you with immediate counseling and also refer you to available sources of medical care, counseling, and other services you may need

You will be in the study for about 1 week, from the time of your Enrollment Visit (today) until your Final Clinic Visit (about 7 days from today), and will use the study gel for a total of 7 days. Most of the visits will take [INSERT APPROXIMATE AMOUNT OF TIME].

It may be necessary for you to make additional visit(s) during your participation in this study to have any of the study procedures listed above repeated in the event of unforeseen or unanticipated abnormal results; difficulties in sample shipping, processing, or testing; and/or if you experience any changes in your physical condition.

ARE THERE ANY RISKS AND/OR DISCOMFORTS?

Risks of Genital Exams

- You may feel discomfort, pressure or embarrassment when your genital area is examined

Risks from Phlebotomy (blood tests)

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

Risks from Dapivirine Gel

If you are in the group receiving dapivirine gel, the gel could cause some side-effects, which are described below. We do not yet know all the side-effects of dapivirine gel and we do not know what effects dapivirine gel will have on you or your penis. Of the 214 women who have used dapivirine gel vaginally, the most common signs and symptoms applicable to men may include the following:

- Headache

- Abdominal pain/discomfort
- Lower abdominal pain
- Blood in urine
- Nausea
- Nasopharyngitis, or inflammation of the nose and pharynx
- Neutropenia; neutropenia is a condition where the number of neutrophils in the blood is too low. Neutrophils are important in defending the body against bacterial infections, and therefore, a person with too few neutrophils is more susceptible to bacterial infections.

The names of some studies in which dapivirine gel was tested for vaginal use include: TMC120-C127/IPM 003, IPM 004, IPM 005B, and IPM 012. The formulation of dapivirine gel being tested in this study is also being tested in IPM 014A and IPM 020.

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
- Learning you have HIV or other infections may cause you to worry or make you nervous. Finding out your HIV status could also cause problems between you and your partner. A trained counselor will help you deal with any feelings or questions you have

[SITES TO INSERT IF APPLICABLE: Your visits will take place in private. It's possible others may learn of your involvement in this research study and treat you unfairly as a result. If you become aware of this please let study staff know and they can provide you with information regarding how to handle situations such as these.]

[SITES TO INSERT IF APPLICABLE: site specific risks, including unknown risks.]

WHAT ARE THE BENEFITS?

You may get no direct benefit from being in this study. **We do not know if dapivirine gel works to protect against HIV.** Also, you may receive the Universal Placebo gel or matched placebo, neither of which contains the study drug.

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 HIV prevention research. This is true no matter what study group you are in.

You will have physical exams and genital 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 at your final clinic visit. If you have infections passed through sex, including HIV infection, you will receive counseling and be referred to a clinic to receive treatment. You may bring your partner here for counseling and referral for testing and treatment for STIs if needed.

WHY MIGHT I HAVE TO STOP USING THE STUDY DRUG?

You may have to stop using gel if you:

- Are unable or unwilling to follow study procedures or instructions
- Could be harmed by continuing to apply the 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 cancelled by the US Food and Drug Administration (FDA), US National Institutes of Health (NIH), the MTN, IPM, the Office for Human Research Protections (OHRP), the other government or regulatory agencies, or the Institutional Review Board (IRB)/Ethics Committee (EC). 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 feel that staying in the study would be harmful to you
- Any 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 that includes all the final clinic exams and tests if the study doctor thinks the exams and tests need to be done. Data collected about you up to the time of withdrawal will remain in the trial database and be included in the data analysis.

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. Regardless of your decision to participate in MTN-012/IPM 010, neither your care nor your relationship will change with [INSERT INSTITUTION NAME] in any way.

WHAT ARE THE COSTS TO ME?

There are no costs to you or your health insurance provider for the study procedures and exams.

WILL I RECEIVE ANY PAYMENT?

You will be compensated for your time and effort for your scheduled study visits and phone calls. You will receive [SITE TO INSERT – SPECIFIC AMOUNT OF MONEY] for each visit. You will receive [SITE TO INSERT – SPECIFIC AMOUNT OF MONEY] for each phone call. 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].

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information private. Your physical and genital 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. 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 learns 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.

Your records may be reviewed by:

- US FDA
- US NIH or their designee
- OHRP
- [INSERT NAME OF SITE] IRB/EC
- Study staff
- Study monitors
- IPM

[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].

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 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. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled.

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 let study staff know.

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 CAB MEMBER [STAFF WILL DECIDE WHICH] at [INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER].

Storage and Future Testing of Leftover Specimens

During your participation in MTN-012/IPM 010 your blood will be tested to check for the health of your blood, liver, kidneys and to see if you have any infections passed through sex. It is possible that after all of the tests above are complete some blood may be leftover. The research doctors want to save any extra blood from your tests during the study. This leftover blood will be kept and used for future research.

If you choose not to have your leftover blood stored for future testing you will still be able to participate in this study. Any leftover blood will be destroyed after all research related tests have been performed.

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 testing 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 IRB or EC whose purpose is to protect you as a research participant.

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.

There are no direct benefits to you, however, people may benefit in the future from your participation. 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 (i.e. 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.

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

Your samples will be stored at facilities at your study site that are designed to store samples securely. The storage facilities are made so that only approved researchers will have access to the samples.

I agree to allow the following leftover samples to be stored for future testing (please initial)

_____ Blood

OR

_____ I do not agree to allow my leftover blood to be stored for future testing

SIGNATURES

Please carefully read the statements below and think about your choice. No matter what you decide it will not affect your relationship with study staff, this institution or the MTN-012/IPM 010 study. Please initial or mark your choice and sign or make your mark below.

[Insert signature blocks as required by the 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

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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-012/IPM 010.

3.1 Essential Documents

The Division of AIDS (DAIDS) policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* specifies the essential documents that study sites must maintain for DAIDS-sponsored studies, including MTN-012/IPM 010. When required documents are modified or updated, the original and all 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. In its policy on *Requirements for Manual of Operational Procedures*, DAIDS requires study sites to establish a standard operating procedure (SOP) for maintaining essential documents. This SOP should be established prior to activation of MTN-012/IPM 010 and should be followed for MTN-012/IPM 010.

Section Appendix 3-1 presents a suggested essential documents filing structure for MTN-012/IPM 010. The suggested structure incorporates guidance received from the DAIDS Prevention Science Program and the DAIDS Clinical Site Monitoring Group. Study sites are not required to adopt the suggested structure, but are encouraged to consider it when developing their filing approach for MTN-012/IPM 010. Further clarifications of the suggested filing structure are as follows:

- Essential documents may be stored in files and/or in binders. The files/binders listed in Section Appendix 3-1 may be further subdivided, consolidated, and/or re-organized if desired.

- It is recommended that a contents sheet be maintained and inserted as the first page(s) of each file/binder. Within each file/binder, it is recommended that documents be filed in ascending date order (most recent documents in front).

- To preserve blinding, certain documents related to the investigational study products will be stored in site pharmacies. A listing of essential documents to be maintained in the pharmacies is provided in Section 3.3, rather than Section Appendix 3-1.

- To facilitate routine inspection by study monitors, certain laboratory-related essential documents should be stored in the main study essential documents files/binders (see Section Appendix 3-1). Other lab-related essential documents (e.g., lab SOPs) may be filed in site laboratories.

- The suggested filing structure assumes that MTN-012/IPM 010 participant case history records will be stored separately from the other essential documents listed in Section Appendix 3-1. Section 3.2 below provides information on the required contents of these records. The suggested filing structure also assumes that the MTN-012/IPM 010 Screening and Enrollment Log, Participant Name-ID Number Link Log, and Clinic Randomization Envelope Tracking Record (which are described in Section 4 of this manual) will be stored in the study clinic or data management area, and not necessarily with the other essential documents listed in Section Appendix 3-1.

3.2 Participant Case History Documentation

Study sites must maintain adequate and accurate participant case history records containing all information pertinent to MTN-012/IPM 010 for each study participant.

3.2.1 Case History Contents

Participant case histories should contain all of the following elements:

- Basic participant identifiers.
- Documentation that the participant provided written informed consent to screen for and participate in the study prior to the conduct of any screening or study procedures, respectively.
- Documentation that the participant met the study's selection (eligibility) criteria.
- A record of the participant's random assignment.
- A record of the participant's exposure to the investigational study products.
- A record of all contacts, and attempted contacts, with the participant.
- A record of all procedures performed by study staff during the study.
- Study-related information on the participant's condition before, during, and after the study, including:
  - Data obtained directly from the participant (e.g., interview responses and other self-reported information)
  - Data obtained by study staff (e.g., exam and lab findings)
  - Data obtained from non-study sources (e.g., non-study medical records)

In addition to the above, DAIDS requires that all protocol deviations be documented in participant records, along with reasons for the deviations, efforts made to correct the deviations, and efforts made to prevent similar deviations in the future. MTN-012/IPM 010 study sites also must report reportable protocol deviations per Section 15.4 of the MTN Manual of Operations.

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 comply with the standards of source documentation specified in the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. The DAIDS policy specifies both requirements and recommendations. Study sites must comply with all requirements and are encouraged, but not required, to comply with all recommendations.

For MTN-012/IPM 010, it is expected that participant case history records will consist of the following source documents:

- Narrative chart notes
- Randomization envelopes and prescriptions documenting participants' random assignments
- 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, Section Appendix 3-2 provides a guide that sites may follow.

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, 5, and 7 of this manual. Detailed information on proper completion of DataFax and non-DataFax forms provided by the MTN SDMC is provided in Section 10 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. For field and outreach workers, participant contacts may alternatively be documented on worksheets or other forms designated for this purpose. 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 should be used to document the following:

- The screening and enrollment informed consent processes (see also Section 4)
- Procedures performed that are not recorded on other source documents
- Study-specific counseling sessions, and any associated referrals, that are not documented on other source documents
- Other pertinent data about the participant that are not recorded on other source documents
- Protocol deviations 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 Good Clinical Practice standards. Sample notes in SOAP format are available from the MTN Coordinating and Operations Center (CORE; FHI) upon request.

Visit Checklists: The checklists in Section 5 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 10 of this manual. The SDMC will provide these forms to each site. The SDMC also will provide study-specific non-DataFax forms to each site. See Section Appendix 3-3 for a listing of all DataFax and non-DataFax forms for this study.

The SDMC will provide all forms in pre-assembled packets for each protocol-specified study visit. Packets of other "as needed" forms also will be provided. The packets will be produced and will be shipped to each study site.

As shown in Section Appendices 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 and enter a note on the form stating the alternate source document used
- 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. To maximize participant confidentiality, the PTID should be used whenever possible, and it is recommended that records that bear names or other personal identifiers, such as locator forms and informed consent forms, be stored separately from records identified by PTID. Any documents transferred or transmitted to a non-study site location — including DataFax 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 should 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.

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

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

- Procedures for assigning PTIDs, linking PTIDs to participant names, and storing the name-PTID link log
- Procedures for establishing participant files/charts/notebooks
- During-visit participant chart and case report form review procedures
- Post-visit participant chart and case report form review procedures and timeframes
- DataFax transmission procedures, including timeframes, case report form storage locations before and after faxing, and mechanisms for identifying when forms have been transmitted
- CASI data collection, back-up, and transmission procedures, including timeframes, CASI equipment storage locations, and mechanisms for identifying when questionnaires have been transmitted
- Procedures for resolving data quality control notes from the SDMC
- Procedures for handling and filing field workers' logs, worksheets, etc.
- Storage locations for blank case report forms
- Storage locations for documents identified by participant names or other personal identifiers
- Storage locations for documents identified by PTID
- Handling of participant study records for off-site contacts and visits
- Confidentiality protections
- Other ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

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

The essential documents listed in Figure 3-1 below should be maintained in study site pharmacies.

Pharmacy staff will document the receipt, dispensing, return, and final disposition of each investigational product used in the study. Separate accountability records must be maintained for product, per instructions provided in the *MTN-012/IPM 010 Pharmacist Study Product Management 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-012/IPM 010 Pharmacist Study Product Management Procedures Manual.* Study clinic staff will contribute to the documentation of product dispensation and chain of custody as described in Sections 4, 5, and 7 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 the double blinding of participants' random assignments, neither study clinic staff nor study participants will be provided access to product-related documentation maintained in the study pharmacies.

Figure 3-1
MTN-012/IPM 010 Essential Documents Maintained in Study Site Pharmacies

- Current MTN-012/IPM 010 protocol
- Current Investigator's Brochure for Dapivirine Gel
- Current Investigator's Brochure for Universal Placebo
- Current MTN-012/IPM 010 FDA Form 1572
- Current list of authorized prescribers to sign MTN-012/IPM 010 prescriptions
- MTN Pharmacy Establishment Plan
- MTN-012/IPM 010 pharmacy and product-related SOPs
- MTN-012/IPM 010 PTID list
- MTN-012/IPM 010 product shipping and receipt documentation
- MTN-012/IPM 010 product storage temperature logs
- MTN-012/IPM 010 investigational product accountability records
- MTN-012/IPM 010 participant-specific and site-specific records (including prescriptions, documentation of product dispensing)
- MTN-012/IPM 010 monitoring visit reports
- MTN-012/IPM 010 communications with site clinic staff
- MTN-012/IPM 010 communications with the MTN CORE (PITT), including the MTN Pharmacist
- MTN-012/IPM 010 communications with the MTN CORE (FHI)
- MTN-012/IPM 010 communications with the MTN SDMC
- Other MTN-012/IPM 010 communications
- Other locally-required administrative, operational, and/or regulatory documentation

3.4 Record Retention Requirements

All study records must be maintained 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, records must be retained for two years after the US Food and Drug Administration is notified that the Investigational New Drug application for the product(s) is discontinued.

All records must be retained on-site throughout the study's period of performance, and for at least three years after completion or termination of the study. Study product records must be stored in site pharmacies, with access limited to authorized study pharmacy staff only, until the study is unblinded. DAIDS will provide further instructions for long-term storage of study records after the study is completed. Study records should not be re-located to an off-site location or destroyed without prior approval from DAIDS.

Section Appendix 3-1
Suggested Filing Structure for MTN-012/IPM 010 Essential Documents

File/Binder #1: MTN-012/IPM 010 Protocol and Current Informed Consent Forms

1. MTN-012/IPM 010 Protocol (including signed and dated protocol signature page): Version 1.0 and any subsequent protocol Clarification Memos, Letters of Amendment, and Amendments
2. Currently-approved (blank) MTN-012/IPM 010 informed consent forms

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

3. Regulatory Authority Correspondence/Authorization/Approval/Notification of the MTN-012/IPM 010 Protocol (if applicable; 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/EC Documentation

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

File/Binder #4: Product Safety Information

8. Investigator's Brochure for Dapivirine Gel: current version and any subsequent updates
9. Investigator's Brochure for HEC Placebo gel: current version and any subsequent updates
10. 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/EC submission of above-listed documents (if applicable) will be maintained in the relevant IRB/EC Files/Binders (i.e., File/Binder #3).

File/Binder #5: MTN-012/IPM 010 Study-Specific Procedures (SSP) Manual

11. Version 1.0 and any subsequent updates

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-012/IPM 010 Study-Specific Standard Operating Procedures

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

File/Binder #7: MTN-012/IPM 010 Staffing Documentation

13. FDA Form 1572 (copy of original form submitted to the DAIDS Protocol Registration Office (PRO), and any subsequent updates)
14. MTN-012/IPM 010 Investigator of Record CV (copy of CV submitted to the DAIDS PRO; ensure that the CV is current prior to initiating MTN-012/IPM 010; it is recommended that CVs be signed and dated to document at least annual updating)
15. Financial Disclosure Forms (original signed and dated forms, and any subsequent updates)
16. Study Staff Roster (copy of original submitted to FHI for study activation, and any subsequent updates)
17. Study Staff Identification and Signature Sheet (if not combined with staff roster; original and any subsequent updates)
18. Study Staff Delegation of Duties (if not combined with staff roster; original and all updates)
19. CVs for Study Staff other than the IoR (ensure that all CVs are current prior to initiating MTN-012/IPM 010; it is recommended that CVs be signed and dated to document at least annual updating)
20. Study Staff Job Descriptions
21. Documentation of Study Staff Training

Section Appendix 3-1
Suggested Filing Structure for MTN-012/IPM 010 Essential Documents

File/Binder #8: Local Laboratory Documentation

22. Local Laboratory Certification(s), Accreditation(s) and/or Validation(s): file documentation current at time of study activation and all subsequent updates
23. 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
24. 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

25. Monitoring Visit Log
26. Monitoring Visit Reports and Documentation of Response to Visit Findings

File/Binder #10: Documentation of Other MTN Site Visits

27. MTN CORE Site Visit Reports and Documentation of Response to Visit Findings
28. MTN SDMC Site Visit Reports and Documentation of Response to Visit Findings
29. MTN Network Lab Site Visit Reports and Documentation of Response to Visit Findings
30. Other Site Visit Reports and Documentation of Response to Visit Findings

File/Binder #11: Study-Related Sponsor Communications

31. Study-Related Communications to and from DAIDS
32. Communications to and from DAIDS Regulatory Support Center (includes copies of all submissions to the DAIDS PRO)

Notes:

- Communications should be filed beginning from the date of DAIDS Protocol Registration
- Communications related to individual MTN-012/IPM 010 study participants will be filed in individual participant study records.

File/Binder #12: Other Study-Related Communications

33. Study-Related Communications to and from MTN CORE
34. Study-Related Communications to and from MTN SDMC
35. Study-Related Communications to and from MTN Network Lab
36. Other Study-Related Communications

Notes:

- Communications related to individual MTN-012/IPM 010 study participants will be filed in individual participant study records.
- As needed to preserve blinding, product-related communications with the MTN Pharmacist will be stored in the study pharmacy.

File/Binder #13: Study Site Staff Meeting Documentation

37. MTN-012/IPM 010 Staff Meeting Agendas, Participant Lists/Sign-In Sheets, and Summaries

Note: Meeting documentation should be filed beginning from the date of Version 1.0 of the protocol

File/Binder #14: Conference Call Documentation

38. MTN-012/IPM 010 Protocol Team Conference Call Summaries
39. Summaries of Other MTN-012/IPM 010 Conference Calls

Note: Conference call summaries will be filed beginning from the date of Version 1.0 of the protocol

File/Binder #15: DAIDS and Other Reference Documentation

40. DAIDS Protocol Registration Policy and Procedures Manual
41. Manual for Expedited Reporting of Adverse Events to DAIDS
42. DAIDS Adverse Experience Reporting System Reference Guide for Site Reporters and Study Physicians
43. US Regulations Applicable to Conduct of MTN-012/IPM 010 (45 CFR 46; 21 CFR 50, 54, 56, and 312)
44. Any other relevant manuals or reference documents

File/Binder #16: Site-Specific Study Activation Documentation

45. Site-Specific Study Activation Notice and supporting documentation

Section Appendix 3-2
Guide to Required Case History Elements and Source Documents for MTN-012/IPM 010

Required Case History Element	Source Documents*
Basic participant identifiers.	Locator form, Demographics form.
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; informed consent coversheet.
Documentation that the participant met the study selection (eligibility) criteria.	Demographics form, locator form; Medical History form*; Concomitant Medications Log form; Physical Exam form; Genital Exam form; local lab logs and result reports§; signed and dated chart notes.
A record of the participant's random assignment.	Clinic randomization envelope tracking record; clinic randomization envelope; study product prescription; pharmacy randomization envelope tracking record; pharmacy randomization envelope; participant-specific pharmacy dispensing record(s).
A record of the participant's exposure to the investigational study products.	Study product prescription; study product returns documentation; participant-specific pharmacy dispensing record(s); dispensed product chain of custody logs; phone reporting system and CASI questionnaires that collect participant-reported product use data.
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; AE Log form; Product Hold/ Discontinuation Log form; Missed Visit form; local lab logs and result reports§; signed and dated chart notes; medical records and other documents bearing information pertinent to the study obtained from non-study sources; other designated site-specific source documents.

*Other site-specific source documents also may be used.

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

Section Appendix 3-3
MTN-012/IPM 010 DataFax and Non-DataFax Forms

MTN-012/IPM 010 DataFax Forms
Demographics
Enrollment
STI Laboratory Results
Laboratory Results
Concomitant Medications Log
Pre-existing Conditions
Physical Exam
Genital Exam
Study Product Returns
Replacement Product Dispensation
HIV Test Results
Interim Visit
Adverse Experience Log
Product Hold/Discontinuation Log
Missed Visit
Termination
Final Clinic Visit
End of Study Inventory

MTN-012/IPM 010 Non-DataFax Forms
Enrollment Eligibility
Behavioral Eligibility
Baseline Medical History Form
Follow-up Medical History Log
Physical Exam
MTN-012/IPM 010 LDMS Specimen

Section Appendix 3-4
Use of MTN-012/IPM 010 DataFax Forms as Source Documents

MTN-012/IPM 010 DataFax Forms	Source?	Comments
Demographics	Yes	Items 1-4 are interviewer-administered; participant responses must be recorded directly onto the form.
Enrollment	No	All items should be completed based on source data recorded on other source documents.
Pre-existing Conditions	No	All items should be completed based on source data recorded on other source documents.
STI Laboratory Results	No	All items should be completed based on laboratory source documents.
Laboratory Results	Mixed	All items except item 2d should be completed based on laboratory source documents. Item 2d may be source.
Concomitant Medications Log	Yes	Form may be source for all items.
Replacement Product Dispensation	No	All items should be completed based on source data recorded on other source documents.
Study Product Returns	Yes	Form may be source for all items.
HIV Test Results	No	All items should be completed based on laboratory source documents.
Physical Exam	Yes	Form may be source for all items.
Genital Exam	Mixed	Form may be source items 1-7. Item 8 should be completed based on source data recorded on other source documents.
Interim Visit	Mixed	Form may be source for item 1. Item 2 should be completed based on source data recorded on other source documents.
Adverse Experience Log	Mixed	Form may be source for items 4-5 and 8-11. All other items should be completed based on source data recorded on other source documents.
Product Hold/Discontinuation Log	Yes	Form may be source for all items.
Missed Visit	Yes	Form may be source for all items.
Final Clinic Visit	Mixed	Form may be source for items 1-4. Item 5 should be completed based on source data recorded on other source documents.
Termination	No	All items should be completed based on source data recorded on other source documents.
End of Study Inventory	No	All items should be completed based on source data recorded on other source documents.

Section Appendix 3-5
Use of MTN-012/IPM 010 Non-DataFax Forms as Source Documents

MTN-012/IPM 010 Non-DataFax Forms	Source?	Comments
Behavioral Eligibility	Yes	Form may be source for all items.
Enrollment Eligibility	Mixed	Form may be source for items 4, 6, and 13. All other items should be completed based on source data recorded on other source documents.
Medical History Log	Yes	Form may be source for all items.
Physical Exam	Yes	Form may be source for all items.

Section 4. Participant Accrual and Enrollment

This section provides information on the requirements and procedures for recruiting, screening, and enrolling participants in MTN-012/IPM 010.

4.1 Study Accrual Plan

MTN-012/IPM 010 will enroll approximately 48 participants with approximately 24 circumcised men and 24 uncircumcised men, across two sites. Stratifying by circumcision status, there will be 12 men in the dapivirine group and 6 participants in each of the two placebo groups. Accrual of all 48 participants is targeted to be completed in 8-12 weeks.

For each site, accrual will begin after the MTN Coordinating and Operations Center (CORE) at FHI issues a written site-specific, study activation notice. Once the study is initiated, accrual will be closely monitored. On a weekly basis, the site will report the number of participants screened (participants who sign the screening IC, regardless of enrollment), enrolled (participants who are randomized to study product, see section 4.2) in the study, and primary reasons for screen failures to CORE (FHI). CORE (FHI) will then distribute a weekly, consolidated, cross-site accrual report to the Protocol Team. The MTN Statistical and Data Management Center (SDMC) will post reports on the ATLAS portal listing the number of participants enrolled in the study based on data received and entered into the study database. Please see Section 13 of this manual for more information on the study reporting plan.

Study staff are responsible for establishing study-specific participant accrual plans and updating these plans and recruitment efforts undertaken to meet site-specific accrual goals, if needed.

Accrual plans should minimally contain the following elements:

- Site-specific accrual targets
- Methods for tracking actual accrual versus target accrual
- Expected screening to enrollment ratios
- 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 and yield 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)
- QA/QC procedures (if not specified elsewhere)

4.2 Screening and Enrollment: Definition and Procedures

The term "screening" refers to all procedures performed to determine whether a potential participant is eligible to take part in MTN-012/IPM 010. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. Required screening procedures are listed in protocol Sections 7.1 and 7.2. Figure 4-1 below provides further operational guidance on the timing of assessment for each eligibility criterion. Screening and Enrollment procedures are detailed in the Visit Checklists (SSP Manual Section 5).

Participants will be considered enrolled in MTN-012/IPM 010 when they have been assigned an MTN-012/IPM 010 Randomization Envelope. The effective point of enrollment is the assignment of the randomized arm (randomization), which occurs at the Enrollment visit.
Further information about randomization can be found in section 4.2.5.

It is the responsibility of the MTN-012/IPM 010 Investigator of Record (IoR) to ensure that only participants who meet the study eligibility criteria are enrolled in the study. Each site must establish a standard operating procedure (SOP) that describes how the IoR, and designated study staff, will fulfill this responsibility. This SOP minimally should contain the following elements:

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

Should site staff identify that an ineligible participant has inadvertently been enrolled in MTN-012/IPM 010, the IoR or designee should contact the MTN-012/IPM 010 management alias list (mtn012mgmt@mtnstopshiv.org) immediately for guidance on subsequent action to be taken

Figure 4-1
Timing of Eligibility Assessments for MTN-012/IPM 010

ELIGIBILITY CRITERIA *For ease of reference, the study eligibility criteria are abbreviated in this figure. Refer to protocol Sections 5.2 and 5.3 for complete specification of the criteria.*	**Assessed at Screening**	**Assessed on day of Enrollment**
Inclusion Criteria		
1. At least age 18	X	
2. Able and willing to provide written informed consent	X	X
3. Able and willing to provide adequate locator information	X	X
4. Able and willing to communicate in written and spoken English	X	
5. HIV-uninfected per Algorithm in Protocol Appendix II	X	
6. In general good health	X	X
7. Willing to abstain from vaginal, oral, and anal intercourse; masturbation, and other activities that may cause irritation or injury to the penis	X	X
8. Willing to abstain from using any genitally-applied preparations	X	X
9. Willing to abstain from non-urgent surgical procedures of the penis/GU area	X	X
10. Agrees to not to participate in other drug trials	X	X
Exclusion Criteria		
1a. Known adverse reaction to any study product or their components	X	
1b. Post-exposure prophylaxis for HIV exposure within 6 months prior to enrollment (a)	X	X
1c. Penile procedures within 42 days of enrollment (a)	X	X
1d. Participation in any other research study within 30 days prior to enrollment (a)	X	X
1e. History of non-gonococcal urethritis and/or STI within 3 months prior to enrollment (a)	X	X
1f. For uncircumcised men, treatment of candidal balanoposthitis/balanitis within 30 days prior to enrollment (a)	X	X
1g. History of recurrent genital dermatosis	X	
1h. Non-therapeutic injection drug use in the 12 months prior to Screening	X	
1i. Current use of immunosuppressant	X	X
1j(i). Hemoglobin <10.0 g/dL (b)	X	
1j(ii). Platelet count <100,000/mm^3	X	
1j(iii). White blood cell count < 2,000 cells/mm^3 (b)	X	
1j(iv). ALT and/or AST > 2.5× the site laboratory ULN (b)	X	
1j(v). Serum creatinine > 1.3× the site laboratory ULN (b)	X	
1j(vi). Creatinine clearance < 80 mL/min (b)	X	
2. Diagnosed with STI or RTI requiring treatment per current CDC guidelines (c)	X	X
3. Has a clinically apparent Grade 1 or higher genital exam finding	X	X
4. Has Grade 1 or higher genital or urinary symptoms	X	X
5. Diagnosed with phimosis or hypospadias	X	X
6. Penile/scrotal piercing or penile tattoos	X	X
7. Has any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives	X	X

Note: This figure presents minimum requirements for each eligibility criterion. Additional assessments related to any criterion may be performed if clinically indicated. All assessments must be conducted within 30 days of providing informed consent for screening.

(a) Although participants are asked about these criteria at Screening, the timeframe specified in the criteria is relative to the day of enrollment.
(b) Otherwise eligible participants with exclusionary test results may be retested during the screening process. If a participant is re-tested and non-exclusionary results are documented, the participant may be enrolled.
(c) Participants diagnosed with a UTI are excluded based on a positive urine culture. If lab results do not confirm a UTI but the participant has symptoms suggestive of a UTI, he is excluded based on exclusion criteria #4.

4.2.1 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place within a 30-day period, beginning on the day the potential participant provides written informed consent for screening. In other words, the day the screening informed consent is signed is counted as "day -30." Enrollment is considered "day 0." For example, as shown below, a potential participant who provides written informed consent for screening on 1 March 2011 could be enrolled on any day up to and including 31 March 2011

March 2011						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1 **Screening Consent (day -30)**	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31 **Last Day to Enroll (day 0)**		

If all screening and enrollment procedures are not completed within 30 days of obtaining written informed consent for screening, the participant must repeat the entire screening process, beginning with the screening informed consent process. Note, however, that a new participant identification number (PTID) is not assigned to the participant in this case (see Section 4.2.5 below). The term "screening attempt" is used to describe each time a participant screens for the study (i.e., each time he provides written informed consent for screening).

4.2.2 Screening and Enrollment Logs

The DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* requires study sites to document screening and enrollment activity on screening and enrollment logs. A sample screening and enrollment log suitable for use in MTN-012/IPM 010 is shown in Figure 4-2. Study sites are encouraged to reference the eligibility criteria item numbers in protocol Sections 5.2 and 5.3 when recording the reason for screening failure/discontinuation on the screening and enrollment logs.

Figure 4-2
Sample Screening and Enrollment Log for MTN-012/IPM 010

MTN-012/IPM 010 Screening and Enrollment Log								
Site Name and Location:								
No. (ex. 1, 2, 3)	Screening Attempt	Screening Date(s)	Participant ID (PTID)	Enrollment date (or NA if not enrolled)	Circumcision Status ("C" or "U" or NA if not enrolled)	Screening Failure/ Discontinuation Date (or NA if enrolled)	Reason for Screening Failure/ Discontinuation (or NA if enrolled)	Staff Initials and Date

4.2.3 Assignment of Participant ID Numbers

The MTN SDMC will provide each study site with a listing of participant identification numbers (PTIDs) for use in MTN-012/IPM 010. As shown in Figure 4-3, the listing will be formatted such that it may be used at each site as the log linking PTIDs to participant names.

Further information regarding the structure of PTIDs for MTN-012/IPM 010 can be found in Section 10 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 he undergoes. Study staff are responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality is maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

Figure 4-3
Sample Site-Specific PTID List for MTN-012/IPM 010

	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			

4.3 Screening HIV Counseling and Testing

Screening HIV testing will be performed using an immunoassay HIV test (either EIA or rapid test) per the algorithm in protocol Appendix II. These tests must be FDA-approved and each site's test kit selections must be validated and approved by the MTN Network Laboratory (NL). Always contact the NL in cases of unusual test results or problems with testing methods. Screening HIV testing will be performed at the Screening Visit:

- If the immunoassay is negative, the participant will be considered HIV-seronegative; no further testing is required.
- If the immunoassay is positive or indeterminate, an FDA-approved Western Blot (WB) or Immunofluorescent Antibody (IFA) test will be performed on the original screening sample (sample 1).
  - If the WB or IFA is negative or indeterminate, contact the NL for guidance.
  - If the WB or IFA is positive for the screening visit, patient is considered seropositive and will not be eligible for enrollment.

Guidelines for performing HIV tests during screening are provided in Section 9 of this manual. All tests must be documented on local laboratory log sheets or other laboratory source documents; such documents must capture the start and end/read times for each test. A second independent clinic or laboratory staff member trained in proper HIV testing and result recording procedures must review, verify, and sign-off on test results within the specified timeframes for the tests and prior to disclosure of results to participants. In addition to initialing or signing the testing logs to document review and verification of the results, the second staff member must also record the time at which the results were reviewed and verified.

HIV pre-test and post-test counseling is required at Screening Visit. Risk reduction counseling is required per protocol at the Screening and Enrollment visits. As part of risk

reduction counseling at the screening visit, male condoms should be offered to all study participants and skills building should be provided to ensure participant understanding of correct condom use. Condoms will not be provided at the enrollment visit as participants are required to remain abstinent during study participation. Referrals also should be provided when indicated. It is generally expected that detailed counselors notes will be completed in order to fully document all counseling sessions and all referrals provided.

All HIV counseling should be provided in accordance with local counseling standards and per site SOPs. Study staff who provide HIV counseling should be trained to do so per local practice standards. Counseling staff should also be trained on study-specific HIV testing methods and interpretation of test results per the testing algorithm in protocol Appendix II.

Pre-Test Counseling and Risk Reduction Counseling:

Client-centered approaches should be used to assess participant knowledge of relevant information, dispel any misconceptions, ensure participant readiness for HIV testing, and ensure participant understanding of test results. Participants should be informed of when their test results will be available. Client-centered approaches should also be used when assessing participant risk for HIV infection and providing risk reduction counseling. The counselor should ask open-ended questions, actively listen to participant responses, probe as needed for further information, and guide the participant in identifying his risk factors and barriers to risk reduction, as well as strategies and action plans to try to address these.

Supported and facilitated by the counselor, the risk reduction plans identified by the participant should reflect and respond to his current risk assessment and should be practical, yet challenge the participant toward risk reduction. Referrals are expected components of risk reduction plans when indicated based on participant needs. When referrals are provided, these should be fully documented in participant study records and should be actively followed up at subsequent counseling sessions to determine whether the participant sought the services to which he was referred, what the outcome of the referral was, and whether additional referrals are needed. All such follow-up should also be fully documented in participant study records.

Post-Test Counseling:

Counselors should provide and explain test results in a private setting per site SOPs. Counselors should assess participant understanding of results and provide clarification and further information as necessary. Regardless of status, continued risk-reduction should be emphasized.

- For negative results, participants should be informed they are not infected with HIV and they are eligible to continue with screening for the study.
- For indeterminate results, participant should be informed that their HIV status is not clear, and that further testing is needed to confirm their status. Counselors should explain the follow-up tests, including the timeframe for results.
- For positive results, participant should be informed that tests indicate they are infected with HIV, and further testing will be done to confirm their status. Counselors should explain the follow-up tests, including the timeframe for results

.

In the event that a participant's status is confirmed as HIV-infected, they should be referred to care per site SOPs.

4.4 Random Assignment

4.4.1 Overview

At both sites, participants will be randomly assigned to three study arms. Participants will be randomized to treatment groups in a 2:1:1 ratio by circumcision status as follows:

Study Group	n, Dapivirine Gel (0.05%)	n, Matched Placebo Gel	n, Universal Placebo Gel
Circumcised	12	6	6
Uncircumcised	12	6	6

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

- MTN-012 Randomization Envelopes for circumcised participants
- MTN-012 Randomization Envelopes for uncircumcised participants
- MTN-012 Randomization Envelope Tracking Records for circumcised participants
- MTN-012 Randomization Envelope Tracking Records for uncircumcised participants
- MTN-012 Prescriptions (Figure 4-3) for circumcised participants
- MTN-012 Prescriptions (Figure 4-4) for uncircumcised participants
- MTN-012 Replacement Randomization Envelopes for circumcised participants
- MTN-012 Replacement Randomization Envelopes for uncircumcised participants
- MTN-012 Replacement Randomization Envelope Tracking Records for circumcised participants
- MTN-012 Replacement Randomization Envelope Tracking Records for uncircumcised participants
- MTN-012 Replacement Prescriptions for circumcised participants
- MTN-012 Replacement Prescriptions for uncircumcised participants
- MTN-012 Site-Specific Pharmacy Dispensing Records

Two series of clinic randomization envelopes will be shipped from the MTN SDMC to each study clinic. One series will be for circumcised participants and one for uncircumcised participants. Randomization Envelopes for circumcised participants will be labeled with the word "CIRCUMCISED." Randomization Envelopes for uncircumcised participants will be labeled with the word "UNCIRCUMCISED." They will be stored in the study site and assigned in sequential order (via increasing envelope number) to participants who have been confirmed as eligible and have provided written informed consent 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 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.

Envelope assignment to eligible participants will be documented on the Randomization Envelope Tracking Record that will accompany each envelope shipment to each site. There will be a Randomization Envelope Tracking Record for each group, circumcised and uncircumcised. The act of assigning a Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once a Randomization Envelope is assigned, the participant is considered enrolled in the study.

Each Randomization Envelope will contain a prescription. Prescriptions will be produced as two-part no carbon required (NCR) forms pre-printed with the site (CRS) name, DAIDS site ID number, site (CRS) location, and randomization envelope number. After recording the PTID and other details on the prescription, clinic staff will separate the two sheets of the form and the white original will be delivered to the pharmacy. The envelope and the yellow copy will be retained in the participant's study notebook in the clinic.

Figure 4-3
Sample MTN-012/IPM 010 Prescription

MTN-012/IPM 010 PRESCRIPTION – CIRCUMCISED

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**	Randomization Envelope #:	**Pre-print**
Randomization Code:	**Pre-print**		

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did participant provide written informed consent for enrollment into MTN-012/IPM 010?..... *yes* ☐ *no* ☐ Clinic Staff Initials: _____

MTN-012/IPM 010 Study Gel
(Dapivirine gel (0.05%), matched placebo gel or universal placebo gel)

Sig: Apply the entire contents of one applicator on to the glans of the penis and then spread to cover the meatus and shaft at night each day for seven (7) consecutive days.

Quantity: Eight (8) pre-filled applicators of study gel

Authorized Prescriber Name (please print):_____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

SAMPLE

Clinic Staff Instructions: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense 1 carton of study gel (8 pre-filled applicators per carton) to the participant.

Clinic Staff Initials: _____

Date clinic envelope opened: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy

Figure 4-4
Sample MTN-012/IPM 010 Replacement Prescription

MTN-012/IPM 010 REPLACEMENT PRESCRIPTION – UNCIRCUMCISED

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**	Replacement Envelope #:	**Pre-print**
Replacement Randomization Codes:		**Pre-print; Pre-print; Pre-print**	

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did participant provide written informed consent for enrollment into MTN-012/IPM 010?..... *yes* ☐ *no* ☐ Clinic Staff Initials:_____

MTN-012/IPM 010 Study Gel
(Dapivirine gel (0.05%), matched placebo gel or universal placebo gel)

Sig: With the foreskin retracted, apply the entire contents of one applicator and coat the glans of the penis and internal foreskin, and then replace the foreskin at night each day for seven (7) consecutive days.

Quantity: Eight (8) pre-filled applicators of study gel

Authorized Prescriber Name (please print):_____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

SAMPLE

Clinic Staff Instructions: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense 1 carton of study gel (8 pre-filled applicators per carton) to the participant.

Clinic Staff Initials: _____

Date clinic envelope opened: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy

Pharmacy Randomization Envelopes will be shipped from the MTN SDMC to the Pharmacist of Record (PoR) at each site 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. They will be stored in the study pharmacy and opened by pharmacy staff upon receipt of a prescription bearing the corresponding Clinic Randomization Envelope number. Assignment of each envelope to an enrolled study participant will be documented on the Pharmacy Randomization Envelope Tracking Record that will accompany each envelope shipment to the site pharmacy. Further information on the contents and management of Pharmacy Randomization Envelopes is provided in the *MTN-012/IPM 010 Pharmacist Study Product Management Procedures Manual*.

4.4.2 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. Random assignment also will take place after the participant has:

- Completed the informed consent process for Enrollment & storage and future testing of specimens
- Completed the CASI Baseline Behavior Assessment
- Provided blood for plasma archive

The in-clinic randomization procedures listed below (Steps C1-C5) then will be performed.

C1. Obtain the next sequential Clinic Randomization Envelope for the appropriate group (i.e. circumcised or uncircumcised) 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 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 Randomization Envelope; alternatively, allow the participant to open it. Remove the prescription from the envelope and verify that the envelope number printed on the prescription corresponds to the envelope number printed on the 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-012/IPM 010 study management team and site Pharmacist of Record (PoR) immediately. Do not proceed with randomization of this or any other participant until instructed to do so by the MTN SDMC.

C3. 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 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 a study staff member authorized in the site's delegation of duties. 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 staff member other than the person who opened the Randomization Envelope, the clinic staff member who completes this section must have access to source documentation of the date upon which the Randomization Envelope was opened.

C4. 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 Randomization Envelope in the participant study notebook. Randomization Envelopes may be hole-punched after they have been opened and their contents have been removed.

C5. Deliver the white original prescription to the study pharmacy. This may be done by the participant or by a study staff member.

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.

4.5 Product Use Instructions, First Product Use, and Adherence Counseling

After random assignment has been completed, participants will be provided with detailed instructions for daily use of their assigned product, followed by adherence counseling.

Participants will be instructed to apply one dose (the entire contents of one applicator) to the glans of the penis and then spread to cover the meatus (the opening of the urethra) and shaft. For uncircumcised participants, they will also be instructed to retract the foreskin and coat the glans and internal foreskin and then replace the foreskin. In addition to verbal instructions, visual aids, such as sample applicators, and genital models, could be used as needed when providing instructions to help ensure participant understanding of proper product use. See section 7 for more details on product use instructions.

Adequate time should be taken to thoroughly explain the product use instructions and answer any questions the participant may have; any questions or concerns raised by the participant should be documented in his study records so this information is easily available for reference at follow-up contacts.

Study product adherence counseling will be provided at the enrollment visit. Counseling will be provided on each of the 8 key messages listed below.

1. **Apply contents of one applicator every day.**
   - At night, before retiring or before the longest period of rest
   - The gel should remain in place for 6-10 hours

2. **If you miss a dose, apply the missed dose on the night following the seventh assigned night.**
   - Contact the clinic to reschedule your follow-up visit to be within 24 hours of your last dose of study product.

3. **Keep your product supplies in your possession.**
   - Do not remove labels from your cartons
   - Avoid mix-ups with others at the clinic
   - Carry your supplies yourself

4. **At home, keep your product supplies in a secure dry place, out of the sun and safe from children.**

5. **Do not share your product and do not use other participant's product.**

6. **Bring all used and unused applicators to the final clinic visit.**

7. **The study staff are here to help and support you. Please contact us if you have:**
   - Problems applying the gel
   - Adverse reactions or safety concerns
   - Problems keeping your gel for your use only
   - Any other problems (such as partner or family issues)
   - If you miss more than one application of the product

8. **Remember, to properly test if the gel is safe, it is very important that you use the gel you are given every day.**

Each counseling session should be fully documented in participant records.

4.6 Informed Consent

Informed consent is a process by which an individual voluntarily expresses his willingness to participate in research, after having been informed of all aspects of the research that are relevant to his 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 — information exchange, comprehension, voluntariness, and documentation — each of which is described below. See Section 4.8 of the International Conference on Harmonization Good Clinical Practice (GCP) Consolidated Guidance (ICH-E6) and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for detailed guidance on the informed consent process and associated documentation requirements.

This study involves two informed consent forms: informed consent for screening; and informed consent for enrollment and storage and future testing of specimens. Participants must document their consent for specimen storage separate from their consent for enrollment by writing their initial or making their mark to indicate whether or not they give their permission to the use and future testing of leftover blood samples. Consent for each is obtained separately, as participants may choose not to consent to specimen storage and still enroll in the study.

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 IoR, and designated study staff, to deliver all required information to potential research participants.

Based on the technical and regulatory reviews that are completed as part of the MTN protocol development and study activation processes, there is adequate assurance that once the MTN CORE (FHI) has activated a site for study implementation, site-specific informed consent forms specify all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It is the responsibility of the IoR and designated study staff to perform the following:

- Deliver all required information in a manner that is understandable to potential study participants: Per eligibility criteria in protocol section 5.2, potential participants must be able and willing to communicate in written and spoken English.
- Assure that informed consent is obtained in a setting free of coercion and undue influence: do not 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 from the study site institution will not be affected by his decision of whether or not to take part in the study.
- Confirm that the participant comprehends the information
- Document the process

4.6.1 Comprehension Assessment

The participant must not be asked to agree to take part in the study, or to sign the informed consent form, until he fully understands the study. Study staff are responsible for implementing procedures to ensure that each participant understands all aspects of study participation before signing the informed consent form.

One approach to assessing comprehension is to use a "quiz" (either oral or written) or other assessment tool which participants complete prior to signing the informed consent form. A sample assessment tool of this type is included in Section Appendix 4-1. Another approach is to use open-ended questions to ascertain participant understanding during the informed consent discussion; some sample open-ended questions that may be used for this study are included in Section Appendix 4-2. For sites that choose to adopt tools such as the samples included in the section appendices, use instructions should be included in the site SOP for obtaining informed consent and the tools should be submitted to the IRB for approval.

Regardless of the method used to assess comprehension, if the assessment indicates misunderstanding of 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 to sign the informed consent form or to enroll in the study. Similarly, if the participant has concerns about possible adverse impacts on him if he were to take part in the study, or indicates that he may have difficulty adhering to the study requirements, do not ask him to sign the informed consent form or enroll in the study unless (or until) such issues can be resolved to the satisfaction of the participant and the IoR (or designee).

4.6.2 Documentation

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

To fulfill this requirement, the participant should print his name, sign, and date the informed consent form in ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a participant's full surname, and it is strongly recommended that initials not be used in place of a participant's full first name. However, if a participant commonly signs his name using an initial for his first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS policy must be met. In order to also meet many of the suggestions listed in the DAIDS policy, site staff may use an informed consent coversheet similar to the example included in Section Appendix 4-3. Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for Source Documentation for MTN-012/IPM 010 and should use the coversheet consistently to document the informed consent process conducted with each participant.

The informed consent process should be documented in a signed and dated chart note. The note (as well as the dates on the informed consent form) should document that informed consent was obtained before conducting any study procedures. The note also should document adherence to the requirements of the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

GCP 4.8.11 requires that participants are given a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this in a chart note and offer the participant an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full informed consent form.

4.6.3 SOP for Obtaining Informed Consent

As a condition for study activation, each 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:

- The minimum legal age to provide independent informed consent at the study site
- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy
- Procedures for providing all information required for informed consent to the participant
- Procedures for ascertaining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures for implementing a change in the version of the informed consent form used
- Staff responsibilities for all of the above

Section Appendix 4-1
Sample Informed Consent Comprehension Assessment Tool for MTN-012/IPM 010

		True	False
1	The main purpose of this study is to find out if dapivirine gel is safe.	☒	☐
2	Each participant will be in this study for 2 months	☐	☒
3	Study participants will have blood tests at the screening visit to test for HIV.	☒	☐
4	Study participants must agree to have blood stored for future testing in order to join this study.	☐	☒
5	Study participants will apply gel twice daily	☐	☒
6	Study participants could become worried or anxious while talking about HIV or waiting for test results.	☒	☐
7	Participants' study records will be available to everyone at the [name of site institution].	☐	☒
8	You may be withdrawn from the study if study staff feel that staying in the study would be harmful to you	☒	☐
9	If you decide not to join this study, you can still come to the [name of site institution] for medical care.	☒	☐
10	If you decide to join this study, you can voluntarily leave the study at any time.	☒	☐

Section Appendix 4-2
Sample Open-Ended Questions for Assessing Comprehension of MTN-012/IPM 010

1. **Please describe your understanding about this study.**
   - ☐ Study objectives
   - ☐ Overall study design: duration, visit schedule, procedures done, options for specimen storage

2. **What do you think you will get out of being in this study?**
   - ☐ HIV/STI education, counseling, and testing
   - ☐ Lab tests
   - ☐ Referrals for care/treatment
   - ☐ Personal satisfaction

3. **Are there aspects of being in this study that concern you?**
   - ☐ Embarrassment/worry/anxiety when discussing HIV/AIDS and risk behaviors
   - ☐ Worry/anxiety while waiting for test results
   - ☐ Discomfort/pain during blood draw
   - ☐ Risks to privacy and possible social harms

4. **What might the study staff do if you miss a study visit?**
   - ☐ Mail, phone, other contacts to re-schedule the visit
   - ☐ Home visits or other community-based contacts to re-schedule the visit
   - ☐ Work through locator contacts to reach the participant

5. **What are some reasons why the study staff might end your participation in the study?**
   - ☐ The study is stopped or cancelled
   - ☐ The staff feels it would be harmful for the participant to stay in the study

6. **What will the study staff do to protect your privacy and confidentiality during the study?**
   - ☐ Conduct visits in private
   - ☐ Keep information about study participation and all study records confidential
   - ☐ Maintain privacy and confidentiality when conducting locator activities
   - ☐ However some “outsiders” may review records

7. **What would you do if you joined the study and then you didn't feel comfortable about the way you were treated in the study?**
   - ☐ Role of IRB/EC and human subjects contact person
   - ☐ Voluntary participation — can leave the study at any time
   - ☐ Voluntary participation — can continue to receive other services at the study site institution

Section Appendix 4-3
Sample Informed Consent Coversheet for MTN-012/IPM 010

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-012/IPM 010.
Date of informed consent process/discussion:	
Start time of informed consent process/discussion:	
Was the informed consent process/discussion conducted according to site SOPs for MTN-012/IPM 010?	☐ Yes ☐ No ⇒ Record and explain departures from site SOPs below.
Can the participant read?	☐ Yes ☐ No ⇒ STOP. Participant is not eligible for MTN- 012.
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 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 5. Participant Follow-up/Visit Checklists

This section provides information on requirements and procedures for participant follow-up in MTN-012/IPM 010. Examples of visit checklists detailing the protocol-specified procedures and data collection forms that must be completed at MTN-012/IPM 010 study visits are also available in this section.

5.1 Study Follow-up Plan and Participant Retention Targets

Once enrolled, each participant will undergo 7 days of study product use, and one additional day of follow-up off study product for a total study duration of approximately 8 days.

As this is a short-term Phase 1 study, a retention rate of 100% is targeted across sites. Further information on retention definitions and procedures for MTN-012/IPM 010 is provided in Section 6 of this manual.

5.2 Types of Follow-up Visits

Scheduled Visits are those visits required per protocol. The protocol specifies that, after Screening and Enrollment visits, participants will have one Follow-up Phone Assessment, and a Final Clinic Visit/Termination Visit.

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 7.6). Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 10 of this manual.

Additional information related to the scheduling and conduct of scheduled and interim visits is provided in the remainder of this section.

5.3 Follow-up Visit Scheduling

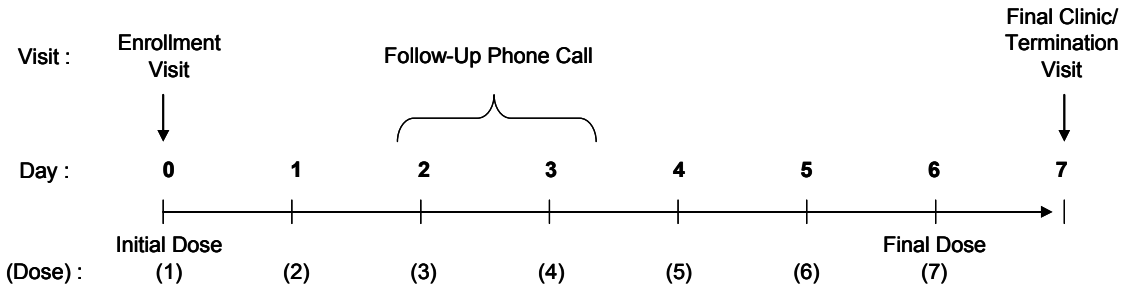
5.3.1 Target Visit Dates and Visit Windows

For MTN-012/IPM 010, randomization is the effective point of enrollment and enrollment is considered Day 0. Enrolled participants will have 2 scheduled visits in MTN-012/IPM 010:

- Follow-up Phone Assessment, targeted within 48-72 hours following enrollment
- Final Clinic Visit (Day 7) /Termination Visit, targeted within 24 hours of final application of study product

Figure 5-1 depicts a timeline of the scheduled follow-up visits for MTN-012/IPM 010 in relation to the 7 days of study product use. Given this schedule, a participant's Final Clinic Visit will be targeted on the same day as enrollment of the subsequent week (i.e. if enrollment is on a Monday, the targeted Final Clinic Visit will be the following Monday). Additionally, 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.

Figure 5-1
Follow-up Visit Schedule for MTN-012/IPM 010



Participants who miss one application of the product should be instructed to complete the missed application on the evening of Day 7, and then present for their final visit within 24 hours following their last dose (Day 8, not shown in figure 5-1). Should a participant miss more than one dose, contact the MTN-012/IPM 010 management team and the MTN-012/IPM 010 Protocol Chair for further guidance.

Acknowledging that it will not always be possible to complete the Final Clinic Visit on the targeted date, a visit window of 7 additional days (through day 14) will be permitted. Study visit windows for MTN-012/IPM 010 are outlined further in Section 10 of this manual.

As MTN-012/IPM 010 is a short term study which includes a pharmacokinetic measurement at the Final Clinic Visit, every effort should be made to schedule participants within the timeframes as specified above. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the visit schedule.

5.3.2 Visits Conducted Over Multiple Days: "Split Visits"

Split visits will not be allowed in MTN-012/IPM 010. All procedures specified by the protocol to be performed at the Final Clinic Visit should be completed at a single visit on a single day. In the event that all required procedures cannot be completed on a single day, contact the management team for further guidance.

5.3.3 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 10 gives detailed information regarding the completion of the Missed Visit form.

5.4 Follow-up Visit Locations

All visits will be conducted at the site clinics. No study specific assessments may be completed off-site. The exception to this is the Follow-up Phone Assessment. Site staff will contact the participant by phone to evaluate if they have experienced any adverse events.

5.5 Study Product Supply/Dispensing during Follow-up

Because of the nature of the short dosing period and follow-up in MTN-012/IPM 010, there will be no routine product re-supplies. The supply of study product at the Enrollment Visit encompasses the full dosing for this study (7 days) plus one extra applicator. Product replacement will occur only in the event of lost or damaged product that must be replaced. For complete details of study product replacement during follow-up please see Section 7.4 of this manual.

5.6 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Section 7 and Appendix I. Further operational guidance on completing protocol-specific follow-up procedures is incorporated into the following sections.

5.6.1 Follow-up Phone Call

Participants should be contacted by phone within 48-72 hours of the enrollment visit to inquire about potential adverse events (AEs). This contact should be documented using the Follow-up Phone Call visit checklist, participant chart notes and/or site-specific forms according to site SOPs.

If indicated, site staff should record reported AEs on the Adverse Experience Log (AE-1) and complete an Interim Visit form (IV-1). If indicated, site staff should schedule an in-person interim visit to follow-up on reported AEs. If permanent discontinuation may be warranted in response to AEs reported over the phone, participants should be instructed to stop product use and be scheduled for evaluation at the study clinic as soon as possible. In this situation, the Product Hold/Discontinuation Log (PH-1) should also be completed to document the temporary hold. Refer to Section 8 for additional guidance regarding AE reporting and management, and Section 10 for data management considerations.

Additional product use instructions, adherence, and/or abstinence counseling can be provided over the phone as needed. All participants should be encouraged to contact the clinic before their next scheduled visit as needed to report symptoms and/or request information or counseling. Staff should also remind participant of final clinic appointment, to bring used and unused applicators, and to record date and time of their last dose for PK.

5.6.2 Final Clinic Visit/Termination Visit

Participants will have one scheduled in-clinic visit during study follow-up. The protocol section 7.4, Appendix I, and the visit checklists provided in this section outline required procedures as well as procedures to be done when clinically indicated. Additional guidance is provided below.

- All used and unused **study product** should be collected from the participant early in the visit. Used product should be counted, documented, and then placed in a biohazard container for destruction in accordance with the sites biohazard materials policy. Unused study product should be counted, documented, and then sent to the Pharmacist of Record (PoR) for documentation and quarantine. NO used applicators should be sent to the pharmacy. Participants should also inform the clinic staff of any used and unused study product that they were unable to bring with them to the clinic (e.g., left at home or thrown away), which should be documented in the chart notes. 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 seven working days after the Final Clinic Visit, the MTN-012/IPM 010 Protocol Safety Review Team (PSRT) must be informed, using the PSRT Query Form. Participants should also communicate the exact date and time (including hours and minutes) of their last product use to the clinic staff. Detailed study product considerations can be found in section 7 of this SSP manual.

- The **Product Acceptability and Adherence Questionnaire (CASI)** should be administered prior to risk reduction counseling. The entire CASI interview must be completed in one sitting. Refer to section 12 for detailed guidance regarding CASI administration.

- **HIV Counseling and Testing** during follow-up will only occur if indicated, based on suspected infection reported by the participant. Due to the short duration and abstinence requirements of MTN-012/IPM 010, it is expected that HIV testing during follow-up will be extremely rare. However, should it be warranted, the algorithm for this testing 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 9 of this SSP Manual.

- **Urine and Blood** should be collected for protocol specified and as-indicated testing per sections 8 and 9 of this SSP Manual. Additional details are also provided in the template visit checklists at the end of this section.

- Updates to **Medical History** and **Current Medications** should be made according to section 8 of this SSP Manual.

- **Physical and Genital Exams** should be conducted according to section 8 of this SSP Manual.

- All identified **AEs** should be documented and reported according to section 8 of this SSP Manual. If an STI or RTI is diagnosed, participants should be referred for treatment per site SOPs. Additional visits may need to be scheduled to follow all

AEs to resolution or stabilization. As needed, sites should provide referrals to care outside the clinic per site SOPs.

- Although the Final Clinic/Termination Visit is the last scheduled study visit, a final contact will be required afterwards to provide the participant with his final laboratory test results, and any post-test counseling, and referral treatment, if needed. Additional contacts also are required for participants with AEs that are ongoing at study exit. 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.

- 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.

5.7 Visit Checklists

5.7.1 Use of Visit Checklists

The visit checklists included in this section (Appendix I) are designed to guide site staff in proper study procedures as well as to serve as source documentation of procedures performed at study visits. Note, however, that checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to:

- Explain why procedures in addition to those listed on a checklist were performed
- Explain why procedures listed on a checklist were not performed
- Document procedures performed at interim visits
- Document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements)

See Section 3 of this manual for detailed information on source documentation requirements. Tips for completing visit checklists in accordance with these requirements are as follows:

- Enter the participant identification number (PTID) and visit date in the top section of each checklist. If information is written on the front and back of the checklist, enter the PTID and visit date on both sides.

- For screening visits, enter the screening attempt number in the top section of the checklist.

- For interim visits, enter the visit code in the top section of the 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 "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why on the checklist (if not self-explanatory); initial and date this entry.

5.7.2 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. Screening procedures are listed in protocol Sections 7.1.

- Informed consent for enrollment must be obtained before any study enrollment or follow-up procedures are performed. Enrollment procedures are listed in protocol Section 7.2. Follow-up procedures are listed in protocol Section 7.3 and 7.4

- On the day of enrollment, random assignment must take place **after** administration of the Baseline Behavioral Computer Assisted Self-Interview (CASI) Questionnaire, collection of blood for plasma archive, and final confirmation of eligibility.

- At the final clinic visit, the CASI Product Acceptability and Adherence Questionnaire must be administered prior to risk reduction counseling.

Section Appendix I
Sample Visit Checklists

PTID:	Visit Date:
Screening Attempt:	Visit Code: 01.0

Initials	Procedures
	1. Confirm identity per site SOPs and determine whether an MTN-012/IPM 010 PTID has previously been assigned to participant.
	2. Determine whether participant is ≥ to 18 years old.
	3. Explain, conduct, and document screening informed consent process per site SOPs.
	4. Assign a MTN-012/IPM 010 PTID (if not done during a previous screening attempt).
	5. Determine last possible enrollment date for this screening attempt: ☐☐ ☐☐☐ ☐☐ DD MON YY
	6. Explain procedures to be performed at today's visit.
	7. Obtain locator information and determine adequacy per site SOPs
	8. Administer Demographics form.
	9. Administer Behavioral Eligibility form
	10. Collect urine (15-60 mL) ❒ Perform dipstick urinalysis for protein, blood, glucose, nitrites and LE; complete testing logs; transcribe results onto Safety Laboratory Results form ❒ Prepare remaining urine for gonorrhea and chlamydia NAAT ❒ If indicated, perform urine culture
	11. Provide and document HIV counseling and testing per site SOPs: ❒ Provide HIV pre-test counseling ❒ Provide HIV/STI risk reduction counseling and condoms ❒ Explain abstinence requirements for study ❒ Collect blood: ❒ 1 x 6 mL lavender top (EDTA) tube ❒ 1 x 5 mL red top (no additive) tube ❒ 1 x 10 mL red top (no additive) tube Volumes shown are approximate. Tailor this item to reflect site-specific tube types and volumes. ❒ Perform and document HIV testing per site SOPs. ❒ Provide HIV test results in the context of post-test counseling

PTID:	Visit Date:
Screening Attempt:	Visit Code: 01.0

Initials	Procedures
	12. Prepare remaining blood for required testing: • Complete blood count with differential and platelets • AST, ALT, creatinine • Syphilis serology
	13. Collect baseline medical history with documentation of current medications; document on relevant source documents and case report forms per site SOPs.
	14. Perform physical exam, including height measurement; document per site SOPs
	15. Perform genital exam; document per site SOPs ❒ Inspect via naked eye and hand-held magnifying glass: ❒ internal and external foreskin (if present) ❒ penile shaft ❒ glans ❒ urethral meatus ❒ scrotum ❒ inguinal lymph nodes (right and left) ❒ gently evert both meatal lips to inspect for discharge ❒ Document all findings on the Genital Exam form.
	16. Determine whether participant has current RTI/STI symptoms.
	17. Provide and explain all available findings and results.
	18. If RTI/STI is diagnosed, refer for treatment per site SOPs
	19. Complete Enrollment Eligibility form
	20. Provide study informational material: [add site-specific list if desired]
	21. Provide contact information and instructions to contact the site for additional information and/or counseling if needed before the next visit.
	22. If applicable, schedule next visit.
	23. Provide reimbursement.

PTID:	Visit Date:
Screening Attempt:	Visit Code: 01.0

Initials	Procedures
	24. Review all visit documentation. *NOTE: The STI Laboratory Results and Laboratory Results CRFs (including 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.*

PTID:	Visit Date:
Screening Attempt:	Visit Code: 02.0

Initials	Procedures
	1. Confirm identity and verify PTID per site SOPs
	2. Confirm that the 30-day screening to enrollment window has not been exceeded for current screening attempt.
	3. Provide and explain all prior screening test results.
	4. Explain procedures to be performed at today's visit.
	5. Review/update locator information and re-assess adequacy per site SOPs.
	6. Explain, conduct, and document enrollment and specimen storage informed consent process per site SOPs.
	7. If indicated, collect urine for urine culture.
	8. Administer Behavioral Eligibility form.
	9. Actively review participant's baseline medical history and current medications. Document all updates on relevant source documents and case report forms.
	10. Perform physical exam; document per site SOPs
	11. Perform genital exam; document per site SOPs ❒ Inspect via naked eye and hand-held magnifying glass: ❒ internal and external foreskin (if present) ❒ penile shaft ❒ glans ❒ urethral meatus ❒ scrotum ❒ inguinal lymph nodes (right and left) ❒ gently evert both meatal lips to inspect for discharge ❒ Document all findings on the Genital Exam form.
	12. Determine whether participant has current RTI/STI symptoms.
	13. Provide and explain all available findings and results.
	14. If RTI/STI is diagnosed, refer for treatment per site SOPs
	15. Review all screening documentation and determine eligibility. Review and update Enrollment Eligibility form

PTID:	Visit Date:
Screening Attempt:	Visit Code: 02.0

Initials	Procedures
	16. Verify participant eligibility per site SOPs
	17. Administer CASI Baseline Behavioral Questionnaire
	18. Collect 10 mL blood in lavender top (EDTA) tube; refrigerate pending delivery to lab for plasma archive.
	19. Complete Enrollment form and LDMS Specimen Tracking Sheet.
	20. Verify documentation of enrollment informed consent and assign next sequential Randomization Envelope to participant per site SOPs. Note: Obtain Randomization Envelope for the appropriate circumcision status.
	21. Complete prescription.
	22. Give completed white original prescription to participant to bring to pharmacy to obtain study product. Retain envelope and yellow copy of prescription in participant's study notebook.
	23. Verify participant received study product. Review product use instructions with participant in detail, using visual aids as needed.
	24. Provide adherence and abstinence counseling per site SOPs.
	25. Provide HIV risk reduction counseling.
	26. Schedule next visit and remind participant to bring all used and unused study product to the Final Clinic visit and to record the exact date and time of last dose prior to final visit
	27. Inform participant of follow-up phone call which will occur in 48-72 hours
	28. Provide contact information and instructions to report symptoms and/or request information, counseling, or study product, before next visit.
	29. Provide reimbursement.

PTID:	Visit Date:
Screening Attempt:	Visit Code: 02.0

Initials	Procedures
	30. Fax all required DataFax forms to SCHARP DataFax: ❒ Demographics ❒ Enrollment ❒ Pre-existing Conditions ❒ Concomitant Medications Log ❒ Genital Exam ❒ STI Laboratory Results ❒ Laboratory Results If applicable: ❒ HIV Test Results

PTID:	Call Date:

Initials	Procedures
	1. Confirm participant identity and PTID per site SOPs
	2. Collect AEs if indicated and document on Adverse Experience Log form
	3. If indicated, schedule interim visit for follow-up of identified AEs
	4. If indicated, instruct participant to stop product use until further evaluation can be completed in the clinic. Document on Product Hold/Discontinuation Log.
	5. If indicated, provide additional product use instructions, adherence, and/or abstinence counseling.
	6. Provide instructions to report symptoms and/or request information or counseling, before next visit.
	7. Provide reimbursement if applicable.
	8. Remind participant of next visit and to: • Bring used and unused applicators • Record the exact date and time of last dose prior to final visit
	9. If applicable, fax all completed DataFax forms to SCHARP DataFax: ❒ Interim Visit (if new AE(s) are reported or updated) ❒ Adverse Experience Log ❒ Product Hold/Discontinuation Log

PTID:	Visit Date:	Visit Code: 03.0

Initials	Procedures
	1. Confirm participant identity and PTID per site SOPs.
	2. Collect used and unused study product; document on the Study Product Returns form.
	3. Explain procedures to be performed at today's visit.
	4. Review/update locator information.
	5. Administer CASI Product Acceptability and Adherence Questionnaire.
	6. Collect urine (15-60 mL) ❒ Perform dipstick urinalysis for protein, blood, glucose, nitrites and LE; complete testing logs; transcribe results onto Safety Laboratory Results form ❒ If indicated, perform urine culture
	7. Provide HIV/STI risk reduction counseling per site SOPs. ❒ If indicated, provide and document HIV counseling and testing per site SOPs ❒ Provide condoms ❒ Collect blood: ❒ 1 x 10 mL lavender top (EDTA) tube ❒ 1 x 6 mL lavender top (EDTA) tube ❒ 1 x 5 mL red top (no additive) tube ❒ 1 x 10 mL red top (no additive) tube Volumes shown are approximate. Tailor this item to reflect site-specific tube types and volumes.
	8. Prepare remaining blood for required testing: • Complete blood count with differential and platelets • AST, ALT, creatinine • Dapivirine level • If indicated, HIV serology
	9. Collect interval medical with documentation of current medications; document on relevant source documents and case report forms per site SOPs.
	10. Perform physical exam; document per site SOPs.

PTID:	Visit Date:	Visit Code: 03.0

Initials	Procedures
	11. Perform genital exam; document per site SOPs ❒ Inspect via naked eye and hand-held magnifying glass: ❒ internal and external foreskin (if present) ❒ penile shaft ❒ glans ❒ urethral meatus ❒ scrotum ❒ inguinal lymph nodes (right and left) ❒ gently evert both meatal lips to inspect for discharge ❒ Document all findings on the Genital Exam form.
	12. Determine whether participant has current RTI/STI symptoms.
	13. Provide and explain all available findings and results.
	14. If RTI/STI is diagnosed, refer for treatment per site SOPs.
	15. If required based on all available information, complete AE Log form(s).
	16. If indicated, schedule next visit.
	17. Provide reimbursement.
	18. Ensure that chart notes and all other required visit documentation is completed.
	19. Fax all required DataFax forms to SCHARP DataFax: ❒ Final Clinic Visit ❒ Study Product Returns ❒ Genital Exam ❒ Laboratory Results ❒ Adverse Experience Log ❒ End of Study Inventory ❒ Termination If Applicable: ❒ Concomitant Medications Log (new and/or updated form pages) ❒ STI Laboratory Results ❒ HIV Test Results

PTID:	Visit Date:	Visit Code:

Initials	Procedures
	1. Confirm participant identity and PTID per site SOPs.
	2. Based on the primary reason for the interim visit, explain procedures to be performed at today's visit.
	3. Review/update locator information.
	4. Review/update interval medical history with documentation of current medications; document per site SOPs.
	5. Collect AEs. If applicable, complete AE Log form(s).
	If indicated, perform procedures in italics below
	6. Perform physical exam; document per site SOPs
	7. Perform genital exam; document per site SOPs
	8. Collect urine (15-60 mL) ❒ *Perform dipstick urinalysis for protein, blood, glucose, nitrites and LE; complete testing logs; transcribe results onto Safety Laboratory Results form* ❒ *Prepare remaining urine for gonorrhea and Chlamydia NAAT* ❒ *Perform urine culture*
	9. Provide and document HIV counseling and testing per site SOPs: ❒ *Provide HIV pre-test counseling* ❒ *Provide HIV/STI risk reduction counseling and condoms* ❒ *Collect blood:* ❒ *1 x 6 mL lavender top (EDTA) tube* ❒ *1 x 5 mL red top (no additive) tube* ❒ *1 x 10 mL red top (no additive) tube* ❒ *Perform and document HIV testing per site SOPs.* ❒ *Provide HIV test results in the context of post-test counseling*
	10. Prepare remaining blood for required testing: • *Complete blood count with differential and platelets* • *AST, ALT, creatinine* • *Syphilis serology*
	11. Provide and explain all available findings and results.
	12. If RTI/STI is diagnosed, refer for treatment per site SOPs

Volumes shown are approximate. Tailor this item to reflect site-specific tube types and volumes.

PTID:	Visit Date:	Visit Code:

Initials	Procedures
	13. Provide study product and complete the Replacement Product Dispensation form.
	14. Review product use instructions
	15. Provide adherence and abstinence counseling per site SOPs.
	16. Schedule or reinforce scheduling of next visit and remind participant to bring all used and unused study product to next visit
	17. Provide contact information and instructions to report symptoms and/or request information, counseling, or study product, before next visit.
	18. Provide reimbursement as needed/indicated.
	19. Ensure that chart notes and all other required visit documentation is completed.
	20. If applicable, fax all completed DataFax forms to SCHARP DataFax: ❒ Interim Visit If applicable: ❒ Concomitant Medications Log (new and/or updated form pages) ❒ Adverse Experience Log ❒ Genital Exam ❒ STI Laboratory Results ❒ Laboratory Results ❒ HIV Test Results ❒ Product Hold/Discontinuation ❒ Replacement Product Dispensation

Section 6. Participant Retention

This section presents information related to definitions, requirements, and procedures for participant retention in MTN-012/IPM 010.

6.1 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-012/IPM 010, retention will be defined based on whether participants complete the scheduled final clinic visit (Day 7) within the allowable visit window. Participants who complete their scheduled visits within the allowable visit window will be considered "retained" for the study. Additional retention measures may be defined and used during the study if desired by the Protocol Chair and/or Protocol Statistician.

The MTN Statistical and Data Management Center (SDMC) will post reports on their ATLAS portal presenting retention rates throughout the period of study implementation. The SDMC also will generate a final end-of-study retention rate after the study is completed. All reports will include site-specific and cross-site information. Please see Section 13 of this manual for more information on the study reporting plan.

6.2 Retention Requirements

As this is a short-term Phase 1 study, a retention rate of 100% is targeted across sites.

The purpose of the 100 percent retention target is to ensure the accuracy of study results. The safety of the study products tested in MTN-012/IPM 010 will be estimated by comparing evidence of Grade 2 or higher male genitourinary adverse event(s) observed among participants assigned to the active product group to the rates observed among participants assigned to the placebo control groups. To avoid bias in the study results, high participant retention rates must be maintained throughout the study.

6.3 Retention SOPs

Site staff are responsible for establishing a standard operating procedure (SOP) for participant retention, and for updating the SOP and retention efforts undertaken to meet the study retention goal of 100 percent. The SOP should minimally contain the following elements:

- Site-specific retention goals
- Methods for tracking actual retention versus retention goals
- Procedures for completing and updating participant locator information
- Site-specific definition of "adequate" locator information (for purposes of determining participant eligibility)
- Visit reminder methods and timeframes
- Methods and timeframes for identifying when a visit has been missed
- Planned retention methods, including what outreach/locator efforts are taken 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)
- QC/QA procedures related to the above (if not specified elsewhere)

6.4 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 visit, and to review/update this information at the enrollment and final clinic visits. 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 study site is encouraged to develop an exhaustive locator form to maximize contact effectiveness and participant retention. Potential locator items include:

- Participant's full name, alias, and/or nickname; government-issued identification number; home address; home phone number; mobile phone number; pager number; work address; work phone number; fax number; e-mail address.

- Name, address, telephone number, and/or other contact information for stable community contacts (i.e., participant family members and friends) who typically know the whereabouts of the participant.

  Note: *Although contact information for a participant's current primary partner likely will be useful, contact information for other contacts 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, etc; participant's child's school and health care provider.

- Name, address, telephone number, and/or other contact information for support groups, shelters, food pantries, and other social service organizations used by the participant.

During the informed consent process and when collecting 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 participant contact 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 (i.e., rather than simply asking "Has any of your information changed since your last visit?"). Also probe for additional information that the participant was not able or willing to provide at previous visits.

6.5 Retention Tips

Some general strategies for maximizing participant retention are as follows:

- Dedicate adequate staff time and effort to retention efforts.
- Work with community members to identify the most applicable contact and retention strategies for the local study population, including the type and amount of participant incentives.
- Keep participants and community members up-to-date on study progress to foster a sense of partnership and ownership of the study
- 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.
- Actively review clinic flow to minimize participant waiting time.
- Develop rapport and ensures participants feel welcome and comfortable during their visits.
- Emphasize the value of the participant's involvement in the study during the study informed consent process.
- Use tracking systems to identify when participants' scheduled visits are due and/or overdue. Establish routine mechanisms to remind both study staff and participants of upcoming scheduled visits.
- Schedule the Final Clinic Visit at the participant's enrollment visit. Give the participant an appointment card with the scheduled visit date and time noted.
- Pay 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 site retention SOPs 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.
- Attempt contact with the participant at different times during the day and the week, including evenings and weekends.
- If a participant wishes to discontinue participation in the study, his wishes must be respected. At the time when the participant states that he wishes to discontinue participation, study staff must document the participant's stated wishes in detail, together with the following information:
    - Why the participant wishes to leave the study.

- Whether the participant is willing to have any further contact with study staff in the future and, if so, through what methods.

- If the participant has any pending laboratory test results, whether and how he is willing to be contacted for purposes of receiving his results.

Section 7. Study Product Considerations for Non-Pharmacy Staff

This section provides information and instructions for non-pharmacy staff related to the ordering and administration of MTN-012/IPM 010 study product for study participants. Associated instructions for the pharmacy staff are provided in the *MTN-012/IPM 010/IPM 010 Pharmacist Study Product Management 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 5 of this manual.

7.1 Responsibilities and Obligations with Regard to Blinding

MTN-012/IPM 010 Investigators of Record (IoRs), and by delegation all MTN-012/IPM 010 study staff, are responsible for maintaining the integrity of the study's blinded design. The identity of the specific gel product to which each participant is assigned is double-blinded, meaning that neither study participants nor study staff — including all members of the Protocol Team — will be provided information on the identity of the specific gel to which each participant has been assigned.

Study documentation maintained by pharmacy staff (such as the documents contained inside the Pharmacy Randomization Envelopes) will include coded information indicating the specific study product to which the participants have been assigned. 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 apply 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 open dispensed product or directly handle individual applicators at dispensing. When used and unused product is returned, clinic staff should only count applicators with minimal visual inspection or handling.

- The unused product should be sent to the pharmacy and placed in quarantine (see *MTN-012/IPM 010/IPM 010 Pharmacist Study Product Management Procedures Manual*).

- The used applicators should be counted and documented and then placed in a biohazard container for destruction in accordance with the sites biohazard materials policy.

- In the event that a participant reports damage or other issues or problems with his study product — other than signs, symptoms, or other adverse events associated with product use — clinic staff should refer the participant to the PoR to further discuss and evaluate his report or concerns. In this type of event, clinic staff should not inspect study product in any way and under no circumstances should clinic staff dispense gel from any applicators

- If study product is damaged or requires the PoR to evaluate the participant's report, the PoR will collect the damaged supplies from the participant (if he has brought them with him to the clinic). If the PoR identifies problems with the participant's applicators or gel, the PoR will immediately inform the MTN CORE Pharmacist of the problem and take action per instructions received from the MTN CORE Pharmacist. The MTN CORE Pharmacist will inform the Pharmaceutical Co-Sponsors, MTN CORE (FHI) Clinical Research Managers, and SDMC Project Managers of the occurrence.

If the PoR has an interaction with a participant regarding study product s/he will document his/her interactions with participants, and any subsequent action taken, in signed and dated detailed notes that are retained in participant-specific pharmacy files. The PoR will forward copies of written documentation, containing no randomization assignment information, to clinic staff to provide information about the participant's report and resolution. Any issues requiring further interventions to reach resolution also should be communicated in writing to clinic staff.

If the PoR dispenses replacement study product supplies to a participant, the PoR will request that clinic staff provide a replacement prescription in order to replace the unusable/damaged applicators.

Blinding will be maintained throughout the study, 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 gel, the IoR may hold or discontinue product use by the participant; however, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an IoR feels that product-specific information is necessary to protect participant safety, he/she should notify the MTN-012/IPM 010 Protocol Safety Review Team (PSRT).

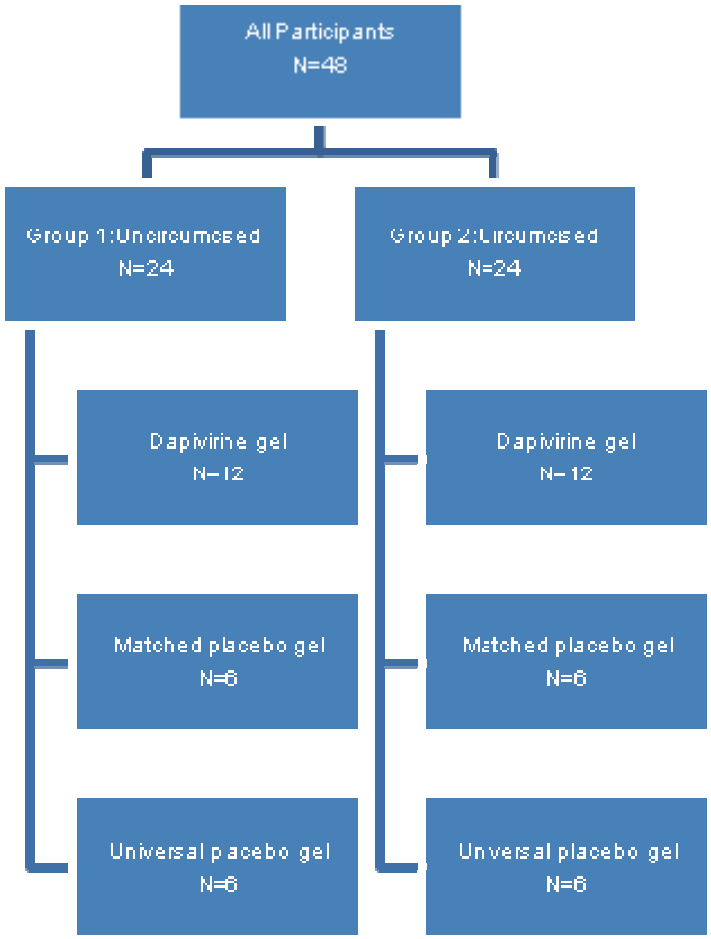
7.2 Study Product Regimens

Men eligible for MTN-012/IPM 010 will be enrolled by groups referred to as Group 1 and Group 2. Group 1 is defined as follows: 24 men that are uncircumcised. Group 2 is defined as follows: 24 men that are circumcised.

Within each Group, men will be randomized in a 2:1:1 ratio to Dapivirine gel, Matched placebo gel, or Universal placebo gel), respectively (see Figure 7-1).

Each participant will apply the content of one applicator of study gel daily for 7 consecutive days.

Figure 7-1
MTN-012/IPM 010 Participant Randomization Scheme



7.3 Dispensing Study Products During Enrollment Visits

Please refer to Section 4 of this manual for further information on procedures for participant randomization and for initial ordering and dispensation of study products for enrolled participants. Instructions for completing MTN-012/IPM 010 Prescriptions are provided in that section.

At the Day 0 Enrollment Visit, upon receipt of a completed and signed MTN-012/IPM 010 Prescription, pharmacy staff will dispense study product for participants per instructions in the *MTN-012/IPM 010/IPM 010 Pharmacist Study Product Management Procedures Manual.* On Day 0 participants will receive 8 pre-filled individually wrapped applicators of gel. The participant will take home 8 applicators. The entire contents of one applicator will be used daily for 7 consecutive days (Days 0-6). Participants will have one extra applicator at home should one dose become unusable for any reason. The applicators will be dispensed in a bag or other container which the PoR will label in accordance with US and local requirements. Labeling will include the PTID of the participant for whom the products were prepared. Participants will be instructed to return both used and unused applicators at their Final Clinic Visit. The used applicators may be placed in a bag provided by clinic staff and the unused applicators may be returned in the container/bag in which they were originally dispensed.

Participant-specific study product may be dispensed directly to participants or to authorized clinic staff who will deliver the applicators to the participant.

At sites choosing to dispense participant-specific study product to clinic staff who will then deliver the product to participants, prescriptions are expected to be delivered to the pharmacy by clinic staff or a runner. Upon receipt of a correctly completed and signed prescription, the PoR will prepare the quantity of study product entered on the prescription.

The MTN-012/IPM 010 Record of Receipt (see Section Appendix 7-1) must be used to document dispensing of participant specific study product to clinic staff. For each Record of Receipt, pharmacy staff will complete the top section (CRS name, DAIDS site ID number, date) and the first four columns in the body of the record. When receiving participant-specific study product from the pharmacy, clinic staff will verify the PTIDs, confirm the quantity of product dispenses for each PTID, and complete the remaining three columns in the body of the record 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 study products dispensed into their custody and ensuring that the products are delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of the products to the designated participants in the participants' study charts. Delivery may be documented in chart notes or on other source documents used for this purpose. In the event that all study products dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the study products to the pharmacy as soon as the participant's visit is completed.

7.4 Dispensing Study Products During Follow-up

The MTN SDMC will provide 24 (12 circumcised and 12 uncircumcised) sealed replacement envelopes to each site. If an enrolled participant requires a replacement carton (i.e., loses or damages his carton) the site clinic staff will assign the participant a replacement envelope. These replacement envelopes will have yellow labels to distinguish them. The replacement envelopes are labeled with the same envelope numbers as the site's first 24 randomization envelope numbers. Clinic staff will choose a replacement envelope with an envelope randomization number and circumcision status that matches the participant's randomization envelope number and circumcision status. Open the replacement envelope and complete the appropriate entry in the Replacement Envelope Tracking Record for the correct circumcision status.

The replacement envelope will contain a prescription with a format similar to the original prescription with the exception that the replacement prescription will be pre-printed with three randomization codes instead of one. Three randomization codes instead of one will allow the pharmacist to locate the appropriate replacement carton to dispense. Complete the replacement prescription and file the "clinic" yellow copy in the participant notebook. Deliver the top white "pharmacy" (original) part of the replacement prescription to the site Study Pharmacist.

7.5 Return of Unused Study Gel Supplies

Protocol Section 9 specifies the circumstances under which use of study product may be permanently discontinued. Protocol Section 6.6 specifies the circumstances under which study product must be retrieved from participants who are required to discontinue product use.

- Participants will be instructed to bring all unused study product to the Final Clinic Visit. The clinic staff will count and document the returned unused study product in the participant's study record on the Study Product Returns CRF. The unused applicators will be sent to the PoR for documentation and quarantine. NO used applicators should be sent to the pharmacy.

- It is anticipated that most participants will have one unused applicator to return. If a participant returns with no study product or more than one unused study applicator, detailed notes documenting the discrepancy should be charted in the participant's chart notes. Because participants are instructed to bring all unused study product to the Final 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 unused product (in most cases this will be one applicator) on the day of the Final Clinic Visit, the remaining product should be retrieved within 7 business days. If the product is not retrieved within 7 business days, clinic staff must inform the PSRT.

7.6 Gel Use Instructions

Study participants will be instructed to apply one dose (the entire content of one applicator), on to the glans of the penis and then spread to cover the meatus and shaft on Day 0 (Enrollment Visit) and continue daily through Day 6. Additionally, uncircumcised men will be instructed to retract the foreskin, coat the glans and internal foreskin, and replace the foreskin. Participants will be instructed to apply the gel at night or before the longest period of rest. The gel should remain in place for 6-10 hours.

Participants who miss one application of the product will be instructed to complete the missed application on the night following the seventh (last) assigned night, and to present to the clinic within 24 hours following their last dose. Participants who miss more than one dose will be instructed to contact the site for further direction.

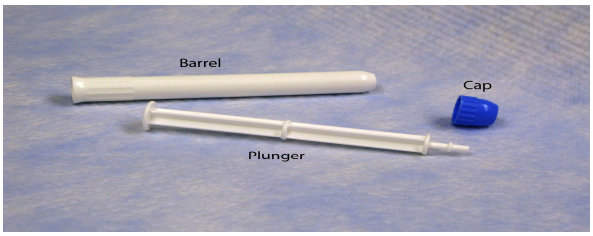
7.7 Instructions for Application of Study Gel for the Participant

Detailed instructions for application of study gel are listed in Figure 7-2 below. For further reference, a listing of frequently asked questions related to product use, and answers to these questions, is provided in Appendix 7-2.

Figure 7-2
Gel Administration Instructions for MTN-012/IPM 010

Removing the Applicator:

- Tear open the wrapper
- Remove the applicator barrel and plunger
- Place the small end of the plunger in the hole of the back end of the applicator (opposite the blue cap)
- Unscrew and remove the blue applicator cap



Applying the Gel:

- Hold the applicator containing MTN-012/IPM 010 study gel in one hand
- Uncircumcised men should retract the foreskin
- Place the tip of the applicator next to the glans of the penis
- Slowly press the plunger all the way into the applicator until it stops, to deposit all of the gel onto the penis
- Spread the gel to cover the glans, meatus and shaft
- Uncircumcised men should also coat the internal foreskin, and replace the foreskin

Storing the Applicator:

- Place the used applicator and cap in the bag provided by the clinic staff; the wrapper may be discarded.
- Return used and unused applicators to the clinic

Appendix 7-1
Record of Receipt

MTN-012/IPM010 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 7-2
Product-Related Scenarios

1. What if the research study staff and/or authorized clinician think there is something wrong with an applicator?

A: If there seems to be something wrong with an applicator (for example, it is difficult to push the study gel out of the applicator, if study gel has leaked out, if the applicator appears to be empty or there is some other problem), do not use the applicator and notify the pharmacy. The unused applicator should be returned to the pharmacy and a new applicator will be dispensed as needed. The MTN CORE Pharmacist should be notified as soon as possible by the Pharmacist of Record.

2. What is the best position to apply the gel?

A: Any position that is comfortable can be used to apply the gel.

3. What should I do if I have trouble applying the gel with the applicator?

A: The applicators should be easy to use. If you have difficulty using the applicators, please contact the study clinic.

4. What happens if I press the plunger too early and most of the gel comes out?

A: If most of the gel comes out other than on the penis (i.e., the floor or elsewhere), discard that applicator and use a new applicator to apply another dose of gel.

5. What happens if the applicators get wet before I use them?

A: If only the wrapper gets wet, the applicator can still be used. Dry the wrapper off before taking out the applicator. If one applicator gets wet, do not use it; rather use the additional applicator provided by the study clinic. If more than one applicator gets wet, contact the study clinic.

6. What should I do if I forget to use the gel?

A: If you miss a dose you should complete the missed application on the night following the seventh (last) assigned night, and then present to the clinic within 24 hours following that last dose. Contact the clinic to reschedule your visit. If you miss more than one dose you need to contact the site for further direction.

7. Will the gel affect my ability to father children?

A: No. The ingredients in the gel are not known to have any effect on male fertility.

8. What should I do if I have a reaction to the gel (e.g., unusual itching, stinging)?

A: Contact the study clinic.

9. **What should I do if the wrapper is already open when I want to use the gel?**

A: You should only use applicators with sealed wrappers, so you should always open the wrapper right before applying the gel. If you notice an applicator with a wrapper that is not sealed, do not use that applicator. Use a different applicator with a sealed wrapper instead. Place the applicator with the unsealed wrapper with your unused applicators and bring it to clinic at the Final Clinic Visit. When you return for the Final Clinic Visit you should inform the study staff of any applicators not used because the wrapper was not sealed. If you find that more than one wrapper is not sealed, please contact the clinic immediately to discuss obtaining a resupply of study product.

10. Can I have sex after I have applied the gel?

A: No, you must abstain from vaginal, oral and anal intercourse (including receptive anal intercourse), even with a condom; masturbation; and other activities that may cause irritation or injury to the penis during study participation.

11: How do I store the gel?

A: Store the gel in a cool, dry place.

Section 8. Clinical Considerations and Safety Monitoring

This section presents information on clinical procedures and safety monitoring performed in MTN-012/IPM 010. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 9. Instructions for completing data collection forms associated with clinical procedures are provided in Section 10.

8.1 Baseline Medical History

The participant's baseline medical 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 history is updated only if the participant recalls information at a later visit that is thought to be relevant.

The baseline medical history should ascertain a participant's medical history and 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 during the course of the study

The non-DataFax Baseline Medical History form is a recommended source document for collecting baseline medical 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 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 has become sexually active. Additional guidelines to collecting the baseline medical history are listed below:

- 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 Male Genital Grading Table for Use in Microbicide Studies (MGGT). If the condition is not listed in the MGGT, refer to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events (hereafter referred to as the "DAIDS Toxicity Table"). See Section 8.14 for further clarifications, guidelines, and tips for severity grading in MTN-012/IPM 010.

- Document medications currently taken for all ongoing conditions on the Concomitant Medications Log form as described in Section 8.4.

8.2 Pre-existing Conditions

All ongoing medical conditions, problems, signs, symptoms and abnormal findings that are observed and/or reported at the time of randomization/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 Enrollment Visit based on all screening and enrollment source documents including, but not limited to, the Baseline Medical History form (non-DataFax), Physical Exam form (non-DataFax), Genital Exam form, Laboratory Results form, and STI Laboratory Results form.

All pre-existing conditions noted at screening and enrollment must be graded. The purpose of grading a pre-existing condition is to 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.

8.3 Follow-up Medical History

It is necessary to update the participant's medical history at the Final Clinic Visit (and any interim visits) in order to determine whether previously reported conditions remain ongoing and whether new symptoms, illnesses, conditions, etc. have occurred since the last medical history was performed. The non-DataFax Follow-up Medical History Log form can be 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.

8.4 Concomitant Medications

The MTN-012/IPM 010 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 preventive medications and treatments (e.g., allergy shots, flu shots, and other vaccinations), 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 history. Site staff should ask open-ended questions to elicit participant report of current medications, and use the information obtained in the medical history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of his medical history, but does not spontaneously list any medications taken for headaches; ask if he 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 history source document.

At the Final Clinic Visit, or during an interim 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 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 history was taken. To further probe for updates, if the participant reports any illnesses, symptoms, etc. since his last medical history, ask whether he 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 inadvertently did not report when providing follow-up medical history information, add the condition to his follow-up medical history source document. To help ensure accurate reporting of concomitant medications information, participants should be encouraged to bring all medications to study visits.

8.5 Prohibited Medications and Products

For MTN-012/IPM 010 the following medications are prohibited from use during the study:

- Immunosuppressive agents, e.g. oral steroids for asthma
- Genitally-applied preparations, except use of usual cleansing products for genital hygiene, other than the study product

Usual cleansing products are any products that the participant regularly uses for genital cleansing purposes, such as soap or cleansing gels. Participants should be counseled to not initiate use of any genitally-applied preparations, including a new cleansing product, during study participation.

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.

8.6 Physical Exam

A physical exam is completed at the Screening, Enrollment, and Final Clinic Visits. It should also be performed at Interim Visits if it is clinically indicated. At all scheduled time points, physical exams should include the assessments listed in protocol section 7.7 and repeated below. Site clinicians may use their discretion to determine whether or not to conduct a more comprehensive 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
- Ear, nose, throat
- Oral mucosa
- Abdomen
- Other components as indicated be participant symptoms

The Physical Exam (non-data fax) form is a recommended source document for recording physical exam findings. The participant's weight should be documented on the Laboratory Results form.

For participants who enroll in the study, ongoing abnormal physical exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits and ongoing at the time of randomization/enrollment 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 below in Section 8.12.

Physical exams may identify additional baseline medical information that participants inadvertently do not report in their baseline medical history. For example, the clinician may identify a skin condition during the physical exam and upon further inquiry learn that the participant has had this intermittent chronic 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.

8.7 Genital Exams

Genital exams are required at the Screening, Enrollment, and the Final Clinic Visits. It should also be performed at Interim Visits if it is clinically indicated.

At all scheduled time points, genital exams should include the assessments listed in protocol section 7.7 and repeated below.

- General inspection via naked eye and hand-held magnifying glass of the following:
    - Entire penile surface

        - Internal and external foreskin (if present)
        - Shaft
        - Glans
        - Urethral meatus
    - Scrotum
    - Inguinal lymph nodes

Genital exam procedures are included in the sample visit checklists provided in Section 5 of this manual.

Potential participants identified at screening or enrollment with a clinically apparent Grade 1 or higher genital exam finding, observed by study staff, and/or participants who report Grade 1 or higher genital or urinary symptoms are not eligible for the study. In addition, participants with penile, scrotal piercing, or penile tattoos observed during the genital examination at screening or enrollment are not eligible for the study. For participants who enroll in the study, abnormal genital exam findings (that are not exclusionary) identified at the Screening and Enrollment Visits and ongoing at the time of randomization/enrollment should be recorded on the Pre-existing Conditions form. Abnormal findings found during genital exams performed during follow-up should be documented and/or reported as described below in Section 8.12.

8.8 STI/RTI/UTI Evaluation and Management

Clinical and laboratory evaluations are performed in MTN-012/IPM 010 to diagnose Urinary Tract Infections and the following STIs and RTIs:

- Chlamydia infection
- Gonorrhea infection
- Syphilis infection

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 8-1 below. Infections should be considered "symptomatic" when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with "signs" of infection that may be observed during clinical examinations performed by study staff.

The presence of symptoms indicative of a possible UTI as well as positive dipstick urinalysis results for either nitrites or leukocyte esterase (LE) should prompt the site to conduct a urine culture. Urinary tract infections (UTIs) will be diagnosed in MTN-012/IPM 010 based on the positive urine culture result. If a site clinician suspects that a participant may have a UTI, but the participant does not have a positive urine culture, the clinician may choose to provide treatment for the UTI. However, the site should not report an AE using the term "Urinary Tract Infection". Instead, each symptom should be reported as its own AE on a separate AE Log form. A positive urine LE or positive nitrites result on dipstick urinalysis should not be reported separately as its own AE. Rather, the positive dipstick results will be captured on the Laboratory Results CRF completed for the visit.

A dipstick urinalysis is required at the Screening and Final Clinic Visits and when clinically indicated at other visits. The following symptoms are considered indicative of a possible UTI and should prompt dipstick urinalysis for nitrites and LE:

- Frequent urge to urinate
- Passage of only a small volume of urine accompanied by sensation of incomplete evacuation
- Pain and burning during urination
- Lower abdominal pain and/or uncomfortable pressure above the pubic bone
- Milky/cloudy, reddish, or bloody urine

Any participant diagnosed with an STI, RTI, or UTI, requiring treatment, during the screening process will be ineligible for the study, per exclusion criteria #2. For enrolled participants, STI/RTI/UTIs diagnosed during follow-up are considered AEs that must be documented, reported and clinically managed.

Figure 8-1
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Chlamydia infection	Most infections are symptomatic and may be accompanied by discharge from their penis or a burning sensation when urinating. Men might also have burning and itching around the opening of the penis. Pain and swelling in the testicles can occur but are uncommon
Gonorrhea infection	Some men with gonorrhea may have no symptoms at all. However, most men have signs or symptoms that appear two to five days after infection; symptoms can take as long as 30 days to appear. Symptoms and signs include a burning sensation when urinating, or a white, yellow, or green discharge from the penis. Sometimes men with gonorrhea get painful or swollen testicles.
Syphilis infection — primary	The classical chancre is a painless indurated ulcer, located at the site of exposure.
Syphilis infection — secondary	Patients may have a highly variable non-itchy skin rash, mucous patches. May include fever, swollen lymph glands, sore throat, patchy hair loss, headaches, weight loss, muscle aches, and fatigue
Syphilis infection — latent	Patients are without clinical signs of infection.

Adapted from CDC STD Fact Sheets: *http://www.cdc.gov/std/general/default.htm*

8.8.1 STI/RTI Treatment

STIs/RTIs will be treated per current CDC guidelines, which can be accessed at:

http://www.cdc.gov/std/treatment/2010/default.htm

Figure 8-2 briefly summarizes current CDC treatment guidelines for each of the infections listed above. In day-to-day practice, the CDC guidelines should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, directly observed single dose treatment regimens should be provided whenever possible.

Figure 8-2
Recommended Treatment Guidelines for STIs/RTIs

STI/RTI	Recommended Treatment
Chlamydia infection	• Azithromycin 1 g orally in a single dose OR • Doxycycline 100 mg orally twice a day for 7 days
Gonorrhea infection	• Ceftriaxone 250 mg IM in a single dose OR, IF NOT AN OPTION • Cefixime 400 mg orally in a single dose OR • Single-dose injectible cephalosporin regimens PLUS • Azithromycin 1g orally in a single dose OR • Doxycycline 100 mg orally twice a day for 7 days
Syphilis infection — primary and secondary	• Benzathine penicillin G 2.4 million units IM in a single dose
Syphilis infection — latent	• Early latent infection: Benzathine penicillin G 2.4 million units IM in a single dose • Late latent infection: Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

8.9 Calculating Creatinine Clearance Rates

Each time a participant's serum creatinine level is tested, his creatinine clearance rate must be calculated, using the Cockcroft-Gault formula:

mL/min = (140 - age in years) x (weight in kg) /72 x (serum creatinine in mg/dL)

To facilitate proper calculation, all sites are encouraged to use the creatinine clearance calculation worksheets provided in the Study Implementation Materials section of the MTN-012/IPM 010 web page.

Sites should enter creatinine results into the worksheet with one decimal place. Participant weight and age should be entered into the worksheet in whole numbers (no decimal places). Once the calculation is complete, sites should print a copy of the worksheet to file in the participant binder.

8.10 Management of Laboratory Test Results

Hematology, liver function, and renal function testing will be performed in MTN-012/IPM 010. For each study participant, the IoR or designee is responsible for monitoring these test results and for ensuring appropriate clinical management of all results. All reviews of laboratory test results should be documented on the flow sheets and/or in chart notes.

In addition to the above, all sites must establish SOPs for reporting and managing critical laboratory values in MTN-012/IPM 010. At a minimum, all test results of severity grade 3 and higher, and all results requiring product discontinuation, should be considered critical and urgently reported to a study clinician; lower grade results also may be considered critical at the discretion of the IoR.

The IoR should routinely review MTN-012/IPM 010 participant study records to ensure proper monitoring and clinical management of laboratory test results, and documentation thereof. All reviews performed by the IoR should be documented in participant study records.

8.11 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for permanent discontinuation of product (Section 9.3), guidance on discontinuation in response to observed AEs (Section 9.4), and management of specific toxicities (Sections 9.5).

Participants will be permanently discontinued from product use for any of the following reasons:

- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use according to the judgment of the IoR/designee
- Participant reports the use of PEP for possible HIV-1 exposure
- Grade 2 AEs judged to be related to study product
- Grade 3 or 4 AEs, regardless of relationship to study product

Due to the short period of study product exposure in MTN-012/IPM-010 participants are not anticipated to be temporarily held from study product for any reason. Therefore, guidance on temporary holds is not provided in the protocol. However, if a participant reports over the phone an AE that may warrant permanent discontinuation, they may be instructed to stop product use temporarily until the AE can be evaluated further at the clinic. In this situation, the Product Hold/Discontinuation Log (PH-1) should also be completed to document the temporary hold.

All specifications of protocol Section 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use in particular.

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Permanent discontinuations must be communicated to site pharmacy staff using the Study Product Request Slip, as described in Section 5 of this manual. Any clinician-initiated product hold or permanent discontinuation must be documented on Product Hold/Discontinuation Log form.

8.12 Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-012/IPM 010. Please also refer to Section 8 of the MTN-012/IPM 010 Protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004, (Clarification Dated August 2009)
- Male Genital Grading Table for Use in Microbicide Studies (Addendum 2)
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, January 2010
- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigators Brochure for Dapivirine gel
- Investigators Brochure for Universal Placebo

8.12.1 Adverse Events

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-012/IPM 010 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.

In MTN-012/IPM 010, all AEs are reportable. That means that all AEs should be recorded on the Adverse Experience (AE) Log form (See Section 10) and the form should be faxed to the MTN Statistical and Data Management Center (SDMC) via DataFax. 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 AE 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.

8.12.2 Serious Adverse Events

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event 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

SAEs are a subset of all AEs. For each AE identified in MTN-012/IPM 010, an authorized study clinician must determine whether the AE meets the definition of SAE, listed above. The Adverse Experience Log case report form includes an item (item 8) to record whether the AE is also an SAE.

8.12.3 Adverse Events Requiring Expedited Reporting

For MTN-012/IPM 010 all SAEs will be reported to DAIDS in an expedited fashion. This includes all SAEs occurring following randomization through the participant's final study contact, regardless of the relationship to the study agents (see Figure 8-3).

Expedited AE reports must be made to the DAIDS Regulatory Support Center (RSC) Safety Office, also known as the DAIDS Safety Office, via the online DAIDS Adverse Event Reporting System (DAERS). If a report needs to be modified or updated, or a 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 SAEs 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 according to the procedures specified in the DAIDS Manual for Expedited Reporting of AEs.

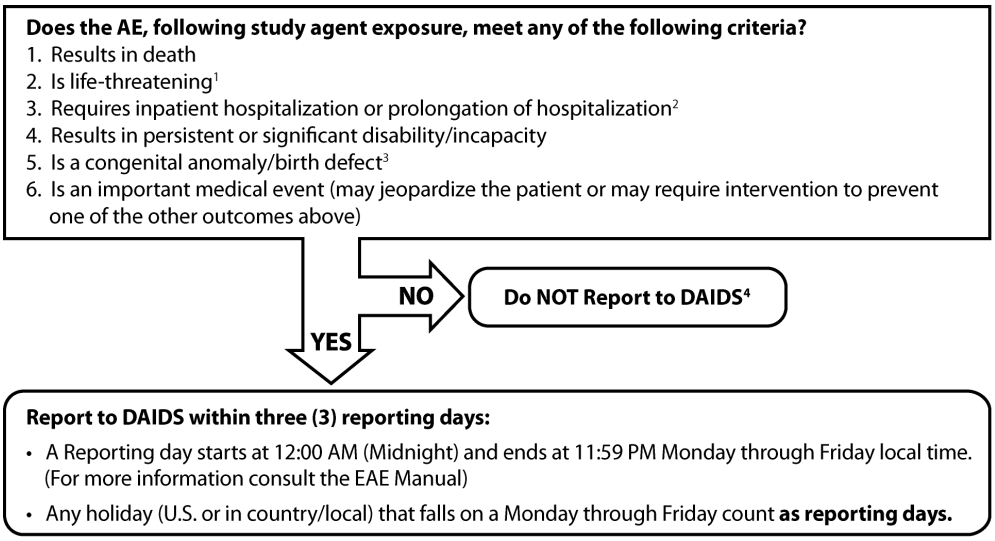
If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) and submitted as specified by the DAIDS Manual for Expedited Reporting of AEs. This form may be found on the Regulatory Support Center (RSC) website at http://rsc.tech-res.com.

For questions or other communications regarding expedited reporting of AEs, 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

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, 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 expedited AE reports 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.

Figure 8-3
Expedited Adverse Event Reporting Requirements for MTN-012/IPM 010



Contact Information for the DAIDS Safety Office:
Website: http://rcc.tech-res.com • **E-mail:** RCCSafetyOffice@tech-res.com
Office Phone: 1-800-537-9979 (U.S. only) or +1-301-897-1709 • **Fax:** 1-800-275-7619 (U.S. only) or +1-301-897-1710
(Office Phone and Fax are accessible 24 hours per day)
Mailing Address: DAIDS Safety Office 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817

[1] "Life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

[2] Per the ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT**: Any admission unrelated to an AE (e.g., for standard labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator. (**NOTE**: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and **would be** reportable.)

[3] Clinically insignificant physical findings at birth, including those regarded as normal variants, do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

[4] Please ensure that any other protocol-specific reporting requirements are met.

8.13 Adverse Event Terminology

Both the Adverse Experience Log case report form and the DAERS report require site staff to assign a term or description to each AE. Whenever possible, a single 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 10 (both on the back of the AE Log form and in Section 10).

8.14 Adverse Event Severity

The term severity is described as the intensity of an AE (that is, the grade or level for a specific event such as mild, moderate, severe, or potentially 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).

Male Genital Grading Table for Use in Microbicide Studies (MGGT) (Addendum 2 of The DAIDS Toxicity Table) 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 Table for Grading Severity of Adult and Pediatric Adverse Events, Version 1.0 December 2004 (Clarification dated August 2009). In cases where an AE is covered in both tables, the MGGT 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 MGGT, the DAIDS Toxicity Table, or in the protocol, sites are to use the 'Estimating Severity Grade' on page 3 of the of the DAIDS Toxicity 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 DAIDS Toxicity Table

8.14.1 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 the upper limit of normal (ULN) or lower limit of normal (LLN), 'normal' values are defined according to local age-adjusted institutional values.

When assessing ULN and LLN values, there will be times when the calculated severity range will have more significant digits than the reported lab value. This may lead to confusion regarding which severity grade to assign. For example, Grade 1 for total bilirubin is 1.1–1.5 times the site lab upper limit of normal (ULN).

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).

8.15 Adverse Event Relationship Assessment

For each AE indentified in MTN-012/IPM 010, 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. When assessing relationship, the study products in MTN-012/IPM 010 that should be considered are the three gels. 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)

8.16 Follow-up Documentation of Adverse Events

All AEs identified in MTN-012/IPM 010 must be followed clinically until the AE resolves (returns to baseline). 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, 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 10.

Likewise, any ongoing SAE that increases in severity to a higher grade than previously reported must be reported again as a new report in DAERS. Ongoing events that improve, but are not resolved and subsequently increase in severity to the same or lower severity grade than previously reported do not have to be reported again to the DAIDS Safety Office.

The requirements for submission of follow-up information on AEs reported to DAIDS are specified in Section 4 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 AE 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
- Additional significant information on a previously reported AE (e.g., cause of death, results of re-challenge with the study agent).

Note: if information regarding an AE reported to DAIDS is updated, 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.

8.17 Outcome of Adverse Events, Review of AE Reports, and Clinician Assessment

The site must follow the progress of each reported adverse event and record eventual outcomes in 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 Final Clinic 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 Final Clinic Visit should be followed clinically until resolution (return to baseline). The Investigator will determine the appropriate follow-up plan for monitoring ongoing AEs at the end of the study and may consult the PSRT for guidance as needed. Clinical management and follow-up after the participant exits the study should be documented in chart notes only (the AE Log form should not be updated once the participant has terminated from the study).

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 source documentation. Results of protocol-specified local laboratory results will also be reported on the Laboratory Result form and if applicable, an Adverse Experience Log form. Sites should document other results if any, in visit chart notes, or in other designated site-specific documents. If any non-protocol-specified lab abnormalities meet AE criteria, these will also need to be reported on an AE Log form. Through the participant's study involvement, lab abnormalities that meet the criteria for expedited reporting to DAIDS must also be 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. He/she must also review and verify the data on the DAERS report for accuracy and completeness. This physician makes the site's final assessment of the relationship between the study product and the adverse event. He/she must electronically sign the completed DAERS report. 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.

8.18 Reporting Recurrent Adverse Events

In the rare occurrence that a resolved adverse event that was previously reported on the AE Log form later recurs, the AE is considered a new adverse event and a new AE Log form must be completed.

Likewise, if a resolved AE that was previously reported to DAIDS later recurs at a level requiring expedited reporting, the AE must be reported as a new EAE Report to the DAIDS Safety Office.

8.19 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.

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. Also report the issue or problem to all responsible IRBs, if required per IRB guidelines.

- Ask the participant to articulate his thoughts on what can/should be done to address the problem, including what he 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 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-012/IPM 010 Protocol Safety Review Team (PSRT) for further input and guidance as needed.

8.20 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-012/IPM 010 protocol for a complete description of the participant safety monitoring procedures in place for MTN-012/IPM 010. Also refer to Section 13 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-012/IPM 010 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 expedited AE reports 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 Medical Officer and IPM Medical Officer will review all DAERS reports received for MTN-012/IPM 010 and follow up on these reports with site staff, the MTN-012/IPM 010 Protocol Team, and drug regulatory authorities when indicated.

- The MTN-012/IPM 010 Protocol Safety Review Team (PSRT) will routinely review safety data reports prepared for MTN-012/IPM 010 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 I for more details).

Management of permanently discontinuing study product 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.

8.21 MTN-012/IPM 010 Protocol Safety Review Team (PSRT)

8.21.1 Roles and Responsibilities of the PSRT

Per the MTN-012/IPM 010 protocol, the roles and responsibilities of the MTN-012/IPM 010 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports. Once the SDMC begins receiving study follow-up safety data, the PSRT will convene via regularly scheduled monthly conference calls. 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 early termination of study participation. The site IoR should consult the PSRT when he/she decides to withdraw a participant from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures.

3. Respond to Investigator queries regarding study eligibility and general AE management and reporting (not necessarily related to product use).

8.21.2 PSRT Composition

The following individuals currently comprise the MTN-012/IPM 010 PSRT:

- Ross Cranston, Protocol Chair
- Lydia Soto-Torres, DAIDS Medical Officer
- Sepideh Habibi, IPM Medical Officer
- Katherine Bunge, MTN Safety Physician
- Devika Singh, MTN Safety Physician
- Molly Swenson, 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 three members, the MTN-012/IPM 010 Protocol Chair, DAIDS Medical Officer (or designee) and the 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 Manager and Prevention Research Specialist, and the SDMC (SCHARP) Project Manager, also will participate in and facilitate PSRT calls and reviews. The DAIDS PSB Program Officer(s), MTN CORE Pharmacist, MTN Network Lab representative, and Co-Sponsors also may attend calls as observers.

8.21.3 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).

Reports will include summary information regarding the number and frequency of events organized by body system (using MedDRA terms) and severity, and will include information on relatedness to study product.

During PSRT conference calls, the DAIDS Medical Officer will summarize any additional DAERS reports received at the DAIDS Safety Office after the cut-off date for inclusion in the SDMC PSRT report.

8.21.4 PSRT Communication

An email distribution list will be used to facilitate communication with the PSRT. Site queries and communications with the PSRT should be sent via email to mtn012safetymd@mtnstopshiv.org. All safety data summary reports from the SDMC will be distributed via mtn012psrt@mtnstopshiv.org.

A standard PSRT query form (Appendix I) will be used to elicit sufficient information to allow the PSRT to make an informed determination and respond to each query. To ensure a timely PSRT response, the MTN-012/IPM 010 Protocol Chair, MTN Safety Physicians 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-012/IPM 010 Protocol Chair, 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 8-I
MTN-012/IPM 010 Protocol Safety Review Team Query Form

Instructions: Email completed form to MTN Safety Physicians: mtn012safetymd@mtnstopshiv.org

IMPORTANT: Complete all required 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
- ☐ On hold
- ☐ Permanently discontinued
- ☐ Not applicable

Has this AE been reported on a SCHARP AE Log form?
- ☐ Yes
- ☐ No

Has this AE been reported as an EAE?
- ☐ Yes
- ☐ No

Has this AE been assessed more than once?
- ☐ Yes
- ☐ No → skip to Comments on page 2

Date of most recent assessment (dd-MMM-yy):

Status of AE at most recent assessment:
- ☐ Continuing, stabilized (severity grade unchanged)
- ☐ Continuing, improving → severity grade decreased to
- ☐ Continuing, worsening → severity grade increased to
- ☐ Resolved

Comments: Provide additional details relevant to this query. If product use has been held, include date of last reported product use prior to the hold (per participant report).

End of Form for Site Staff. Email completed form to the MTN-012/IPM 010 Protocol Safety Physicians, mtn012safetymd@mtnstopshiv.org. If an email response is not received from the PSRT within 3 business days, re-contact the Protocol Safety Physicians, copying the study management team (mtn012mgmt@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 9. Laboratory Considerations

9.1 Overview and General Guidance

This section contains information on the laboratory procedures performed in MTN-012/IPM 010.

As transmission of HIV and other infectious agents can occur through contact with contaminated needles, blood, and blood products, 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 can be found at the following website:

http://www.cdc.gov/hai/

Laboratory procedures will be performed at various locations in site clinics or laboratories, MTN Network Laboratory (NL), or PRA International laboratory in the Netherlands. Table 9-1 and table 9-2 highlight specimen and storage requirements. Additionally, appendix 9-3 summarizes information for specimen requirements.

Regardless of whether tests are performed in clinic or laboratory settings, study staff that performs the tests must be trained in associated 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 (e.g., PNL, IQA, VQA) to monitor and certify laboratories for testing. US Laboratories that are certified by CLIA (Clinical Laboratory Improvement Amendment) will be able to substitute this for some of the documentation requirements required of other labs. Valid CLIA certificates must be provided in these cases.

Table 9-1
Overview of Laboratory Testing Locations, Specimens, and Methods for MTN 012

Assay or Process	Testing Location	Specimen Type	Tube/ Container	Size of Tube Recommended[2]	Kit/Method/Special arrangement
Urine NAAT for gonorrhea and Chlamydia	MTN Network Lab Regional or site lab	Urine	Plastic screw top Cup, Urine Preservative Tube		BD Probetec or Genprobe Aptima
Dipstick Urinalysis[1]	Clinic/Local lab	Urine	Plastic screw top cup		FDA approved test
HIV antibody screen and Western Blot	Clinic/Local Lab	Plasma or whole blood (serum acceptable)	EDTA or plain tube	4 mL	FDA approved tests
Complete blood count with Differential and Platelet	Local Lab	Whole Blood	EDTA tube	4 mL	Not specified
Chemistries (AST, ALT, Creatinine)	Local Lab	Serum	Plain or serum separator	4 mL	Not specified
Blood Dapivirine level	PRA International (Netherlands lab)	Plasma	EDTA Tube	10 mL	PRA International (Netherlands lab)
Plasma Archive	Clinic/Local Lab	Plasma	EDTA Tube	10 mL	Store frozen plasma until study team requests shipping and/or testing
Syphilis Serology	Local Lab	Serum or Plasma	EDTA tube, plain or serum separator	4 mL	Not specified

[1] Perform Urine Culture as indicated if local standard of care. Dipstick tests are glucose, blood, protein, leukocytes, and nitrites.
[2] Draw the suitable tube size or number of tubes to assure that minimum volumes are met.

Table 9-2
Overview of Specimens for Storage and Shipment

Specimen	Additive	Ship to:	Shipping schedule
Plasma for storage	EDTA	MTN Network Lab	Store at site until notified by MTN[1]
Blood Dapivirine level	EDTA	MTN Network Lab	Store at site until conclusion of study[1]

[1]At the time of shipment, the MTN NL will furnish shipping instructions and addresses.

Sites are responsible to ensure that specimen volumes collected 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. These blood draws will vary by site. Ideally, one method, type of test kit, and/or combination of test kits will be used for each protocol specified test throughout the duration of the study. If for any reason a new or alternative method or kit must be used after study initiation, site laboratory staff must perform a validation study of the new method or test prior to changing methods. The MTN NL must be notified before the change (for non-CLIA certified labs) and can provide further guidance on validation requirements. Similarly, all labs (including CLIA certified labs) must contact the MTN NL in cases of changes to normal ranges.

Provided in the remainder of this section is information intended to standardize laboratory procedures across sites. Adherence to the specifications of this section is essential to ensure that data derived from laboratory testing will be considered acceptable to all regulatory authorities across study sites. This section of the MTN-012/IPM 010 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 site Standard Operating Procedures (SOPs).

9.2 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. Study sites will be provided with pre-printed labels or a template that can be used to generate labels. The date the specimens are collected should also be included on the label. If the date is handwritten, it should be in indelible ink (such as a Sharpie pen).

When specimens are tested at the local lab, any additional labeling required for on-site specimen management and chain of custody will be performed in accordance with site SOPs. The stored plasma specimens will be entered into LDMS and labeled with LDMS-generated labels.

9.3 Procedures for Specimens that can not be evaluated

Specimens will be redrawn or recollected if it is found that they can not be evaluated per site SOPs. Sites will monitor specimen management problems as part of ongoing Quality Assurance. In cases where additional specimens need to be recollected either due to a laboratory error (lost or broken specimen or clerical error) or clinic error (clerical error), a protocol deviation form may be required per the MTN Manual of Operations: http://www.mtnstopshiv.org/node/187.

9.4 Use of LDMS

The Laboratory Data and Management System (LDMS) is a program used for the storage and shipping of laboratory specimens. It is supported by the Frontier Science Foundation (FSTRF). LDMS must be used at all sites to track the collection, storage, and shipment of specimens in MTN-012/IPM 010: plasma archive and plasma samples for Dapivirine levels.

Detailed instructions for use of LDMS are provided at: https://www.fstrf.org/ldms (may require a password).

All sites will be required to maintain the current version of LDMS and monitor updates relating to use of the LDMS. It is crucial to be aware of proper label formats to ensure that specimens are correctly labeled. Sites will be responsible to back up their LDMS data (frequency determined by site) locally and to export their data to FSTRF (at least weekly).

Questions related to use of LDMS in MTN-012/IPM 010 may be directed to the MTN Network Laboratory 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

Each site must export its LDMS data to Frontier Science (FSTRF) on a weekly basis. Exported data are used by the MTN SDMC (Statistical Data and Management Center) to generate a monthly specimen repository report and to reconcile data entered in LDMS with data entered on study case report forms. Any discrepancies identified during the reconciliation are included in a monthly discrepancy report for each site. Sites are expected to resolve all discrepancies within two weeks of receipt of the report. The MTN NL is responsible for reminding sites to adhere to the two week timeframe and for following up with sites that do not resolve discrepancies within two weeks. The MTN SDMC reviews the discrepancy reports for critical samples (e.g., plasma needed for confirmatory HIV testing) that appear to be missing, and works with the NL and site staff to undertake appropriate corrective action. All corrective action should be documented in paper-based clinic and/or laboratory records as appropriate, and entered in the details section of LDMS. The NL and SDMC will discuss and document any items that, although resolved, appear 'irresolvable' in LDMS.

Table 9-3
LDMS Specimen Management Guide to Logging in MTN 012 Specimens

Test	Primary	Additive	Derivative	Sub Add/Derv	Primary Volume	Aliquot Volume	Units
Plasma for storage	BLD	EDT	PL1/2	N/A	Variable	1-2[1]	mL
Plasma for Dapivirine	BLD	EDT	PL1/2	N/A	Variable	1.25-2[2]	mL

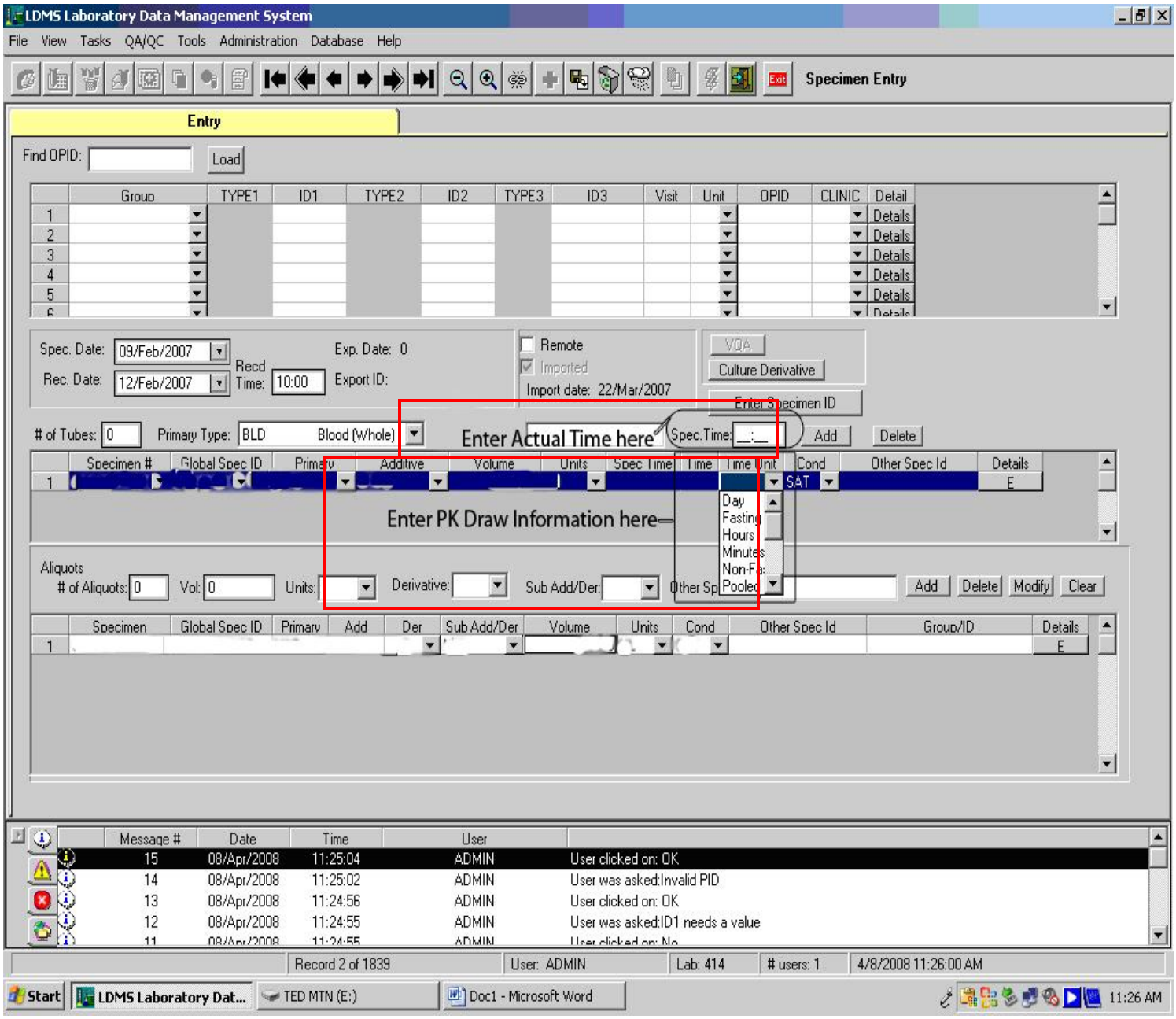
[1] Prepare as many 1mL to 2 mL aliquots as possible with a total volume of all aliquots ≥ to 4 mL.
[2] Prepare two tubes with a minimum of 1.25 mL (up to 2mL) and label one as "primary sample" (to send to NL) and the other as "back-up sample" (stored at site).

The table above should be used as a guide when logging in MTN 012 specimens. Please use the LDMS codes listed above 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 9-1 for a copy of the LDMS tracking sheet.

Logging in PK Samples

- Enter the actual time in the Specimen Time area (See Image 1)
- Enter the PK time point information in Time and Time Unit area (See Image 1)

IMAGE 1: LDMS Entry Screen



9.5 Urine Testing

The urine tests performed at each study visit will depend on the visit and the clinical presentation of the participant. In general, at study visits when urine testing is required, a single specimen will be collected and then 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.

9.5.1 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.
- 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 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 Urine Preservation Tube (UPT) for subsequent chlamydia and gonorrhea testing.

9.5.2 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, blood, protein, leukocytes and nitrites. If leukocytes or nitrites are positive, perform 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.

9.5.3 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 GenProbe 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 STI Laboratory Results case report form..

9.6 Blood Specimens for HIV testing, Syphilis, Hematology, Chemistries, Blood Dapivirine, and Plasma Archive

The blood tests performed at each study visit vary depending on the visit and potentially the clinical presentation of the participant. Perform all tests according to site SOPs and package inserts.

9.6.1 Specimen Collection and Initial Processing

Label all required tubes with a SCHARP-provided PTID label at the time of collection. After collection:

- Allow plain tubes (no additive or serum separator tubes) to clot, then centrifuge per site SOPs to yield serum for syphilis and chemistries.
- EDTA Tubes should be gently inverted at least eight times after specimen collection to prevent clotting. EDTA tubes are used for hematology, HIV testing, plasma archive, and Dapivirine Level. If whole blood for hematology testing and plasma are to be taken from the same tube, the hematology must be completed before the tube is centrifuged and aliquoted. If whole blood is to be used for multiple tests, ensure that the tube is well mixed before removing any specimen.

9.6.2 HIV Testing

EDTA plasma (whole blood and serum are also acceptable) will be tested for HIV using tests that have been validated at the study site. All HIV testing in laboratories must be done under Clinical Laboratory Improvement Amendment (CLIA) certification. All tests and associated QC procedures must be documented on local laboratory log sheets or other laboratory source documents.

HIV infection status will be assessed using an FDA-approved HIV immunoassay per the MTN-012/IPM 010 HIV testing algorithm (see appendix 9-2 in this section of this MTN-012/IPM-010 SSP or appendix II of the MTN-012/IPM-010 protocol). If the screening test is negative, the participant will be considered HIV-seronegative. If the screening test is positive or indeterminate, an FDA-approved Western Blot (WB) or Immunofluorescent Antibody (IFA) test will be performed on the original screening sample (Sample 1). If there is insufficient sample to perform WB or IFA, then additional blood must be recollected and must still be regarded as screening Sample 1 per the algorithm. If the WB or IFA is negative or indeterminate, contact the NL for guidance. If the WB or IFA is positive for the screening visit, patient is considered seropositive and will not be eligible for enrollment. If the WB or IFA is positive for any other visit, a second specimen (Sample 2) will be drawn for confirmatory testing. If the WB or IFA is negative or 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.

9.6.3 Syphilis Testing

Syphilis testing will be performed using an FDA approved rapid plasma reagin (RPR) screening test followed by a confirmatory test for Treponema pallidum. Any FDA approved Treponema pallidum confirmatory test can be used such as the microhemagglutinin assay for Treponema pallidum (MHA-TP), Treponema pallidum hemagglutination assay (TPHA), Treponema pallidum particle agglutination (TP-PA), or fluorescent treponemal antibody (FTA-ABS). All positive RPR results must have a titer obtained and reported. RPR tests may be performed on either serum or plasma. Serum is the specimen of choice for syphilis confirmatory tests, however other sample types may be allowed according to the particular tests package insert. 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. If a confirmation test is positive, then the participant will not be eligible for enrollment. Appropriate 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-012/IPM 010 Protocol Safety Physicians (mtn012safetymd@mtnstopshiv.org).

9.6.4 Hematology Testing

Complete blood counts will be performed at all sites according to protocol at the Screening and Final Clinic Visits.

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 SOP's.

9.6.5 Serum Chemistries

Liver Function

- Aspartate aminotransferase (AST)
- Alanine transaminase (ALT)

Renal Function

- Creatinine (Calculated creatinine clearance is determined each time serum creatinine is done). Formula (for males): mL/min = (140 - age in years) x (weight in kg) /72 x (serum creatinine in mg/dL). The Creatinine Clearance Calculator is located at the MTN website in the Study Implementation Materials section of the MTN-012/IPM protocol.

These chemistry tests will be performed on serum per local SOP's.

9.6.5 Plasma archive

For plasma archive, collect blood into a labeled 10 mL EDTA Vacutainer tube using either an indwelling venous catheter or direct venipuncture. Plasma will be stored at ≤ -70°C and batched onsite until the MTN-012/IPM 010 study team requests shipping and/or testing.

- 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 1mL to 2 mL aliquots in cryovials as possible with a total volume of aliquots greater than or equal (≥) to 4 ml. If less than 4 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.

9.6.6 Plasma Dapivirine Level

At the Final Clinic Visit, collect blood into a labeled 10 mL EDTA Vacutainer tube using either an indwelling venous catheter or direct venipuncture.

1. Mix blood sample with the anticoagulant using gentle inversions (8 to 10 times).
2. Centrifuge the sample at approximately 3000 rpm (1500 x g) for 10 minutes. The centrifugation should be completed within 2 hours of blood collection.
3. Use a pipette to aliquot approximately 1.25-2.0 mL of the resulting plasma into two separately labeled 5 mL polypropylene tubes or 2 mL cryovials. One of these will serve as the primary sample; the second will serve as a back-up in case the primary samples are accidentally destroyed during shipment to MTN NL or PRA, the bioanalytical lab in the Netherlands.
4. Prepare two storage boxes and label one as "primary samples" and the other as "back-up samples". Transfer the tubes from each participant in chronological order into the storage boxes. All samples will be tracked in LDMS.
5. Store the boxes with samples at ≤-20˚C until shipped to MTN NL. MTN NL will ship all primary samples as one batch to PRA at conclusion of study.
6. Prior to shipping, prepare a shipment box (a foam chest) filled with dry ice sufficient for a 24 hour period with an appropriate shipping label.

NOTE: Remember to only ship one set of samples to MTN NL. The back-up samples will be shipped to PRA in a separate shipment, at the direction and with the prior approval of MTN NL, after confirmation that the original samples arrived safely at PRA.

Appendix 9-1
LDMS Tracking Sheets

MTN-012/IPM 010 LDMS Specimen Tracking Sheet (non-DataFax)

For login of MTN-012/IPM 010 stored specimens into LDMS

Participant ID ☐☐☐-☐☐☐☐☐-☐ (Site Number / Participant Number / Chk)

Visit Code ☐☐.☐

Specimen Collection Date ☐☐ ☐☐☐ ☐☐ (dd / MMM / yy)

# of TUBES or SPECIMENS	PRIMARY SPECIMEN	PRIMARY ADDITIVE	ALIQUOT DERIVATIVE	ALIQUOT SUB ADDITIVE/ DERIVATIVE	NOTES FOR LAB
☐	Blood **(BLD)** *Plasma* **Collection Time:** __ __ : __ __ *hour : min*	EDTA (purple top)	PL1/2	N/A	Prepare as many 1mL to 2 mL aliquots as possible with a total volume of aliquots greater than or equal to 5mL. If at room temp, freeze within 2 hours. If refrigerated or on ice after collection, freeze within 24 hours of collection.
☐	Blood **(BLD)** ***Dapivirine level*** **Collection Time:** __ __ : __ __ *hour : min*	EDTA (purple top)	PL1/2	N/A	Transport to lab and process within 2 hours. Prepare 2 tubes and label one as "primary sample" and the other as "back-up sample". Freeze immediately after centrifugation.

Comments: _____

Initials: _____ (Sending Staff) _____ (Receiving Staff) **LDMS Data Entry Date:** ☐☐ (dd) ☐☐☐ (MMM) ☐☐ (yy) / _____ (LDMS Staff)

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Note about LDMS Tracking Sheet: The minimum volume for plasma archive has been changed to 4 mL. The printed tracking sheets at the sites do not reflect this change.

MTN-012/IPM 010 LDMS Specimen Tracking Sheet (non-DataFax)

For login of MTN-012/IPM 010 stored specimens into LDMS

Purpose: This non-DataFax form is used to document collection and entry of MTN-012/IPM 010 blood specimens into the Laboratory Data Management System (LDMS).

General Information/Instructions: A copy of this form accompanies enrollment plasma and PK blood specimens (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.
- **NUMBER OF TUBES COLLECTED:** In the box to the left of each additive type, record the total number of tubes collected. 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.

Appendix 9-2
ALGORITHM FOR HIV ANTIBODY TESTING FOR SCREENING AND ENROLLED PARTICIPANTS

Appendix 9-3
Specimen Requirements Overview

MTN-012/IPM 010 LAB SPECIMEN PROCESSING GUIDELINES- Urine Specimens

Assay	Primary Specimen	Additive/Container	Minimum Volume	Testing Specifications	Handling Requirements
NAAT for GC/CT	Urine	Collect in a Urine Container (no additive) and transfer to Urine Preservative Tube	4 ml	MTN NL or Locally: batched 2-3 times per week	Follow package insert directions for handling requirements
Dipstick Urinalysis	Urine	Urine Container- No additive	Enough to cover strip	Locally in real time	Room temp-analyze within 2 hours of collection
Culture	Urine	Urine Container (Sterile) - No additive	N/A	Locally in real time	Locally Defined

MTN-012/IPM 010 LAB SPECIMEN PROCESSING GUIDELINES- Blood Specimens

Assay	Primary Specimen	Additive/Container	Minimum Volume	Testing Specifications	Handling Requirements
Creatinine, AST and ALT	Blood	Plain Tube-No additive or Serum separator tube (locally defined)	Locally defined	Locally in real time	Locally Defined
Syphilis Serology	Blood	Plain Tube-No additive or Serum separator tube (locally defined)	Locally defined	Locally in real time	Locally Defined
Full Blood Count	Blood	EDTA Tube	Locally defined	Locally in real time	Locally Defined
HIV-1 Test	Blood	EDTA Tube	Locally defined	Locally in real time	Locally Defined
Dapivirine Level	Blood	EDTA Tube	1.25 mL plasma/aliquot	Stored and shipped for analysis in batches.	Transport to lab and process within 2 hours. Prepare two tubes and label one as "primary sample" and the other as "back-up sample". Freeze immediately after centrifugation.
Plasma Archive	Blood	EDTA Tube	4 mL plasma	Stored and shipped for analysis in batches.	Prepare as many 1mL to 2 mL aliquots as possible with a total volume of aliquots ≥ to 5mL. If at room temp, freeze at -20°C within 2 hours. If refrigerated or on ice after collection, freeze within 24 hours.

Section 10. Data Collection

The purpose of this document is to provide site staff with the information they need to successfully complete and submit MTN-012/IPM 010 case report forms. For questions about this section or about general data collection policies, procedures, or materials, please contact Corey Miller (corey@scharp.org).

For this study, the SDMC (Statistical and Data Management Center) is SCHARP (the Statistical Center for HIV/AIDS Research and Prevention). SCHARP is located in Seattle, WA, USA, and is in the US Pacific Time (PT) time zone. The SCHARP MTN-012/IPM 010 team members, along with their job roles and e-mail addresses, are listed below.

Role on MTN-012/IPM 010	Name	E-mail address
Protocol Statistician	Liza Noonan	liza@scharp.org
Project Manager	Corey Miller	corey@scharp.org
Statistical Research Associate	Marla Husnik	marla@scharp.org
Statistical Research Associate	Jason Pan	zpan@scharp.org
Clinical Affairs Safety Associate	Molly Swenson	mollys@scharp.org
Protocol Programmer	Dara Mendyuk	dara@scharp.org
Reporting Programmer	Cathy Kirkwood	ckirkwoo@scharp.org
Laboratory Programmer	Della Wilson	della@scharp.org
CASI Programmer	Lynda McVarish	lmcv@scharp.org
Data Coordinator	Suzanne Cullers	scullers@scharp.org
Document Specialist	Lori Filipcic	lorif@scharp.org

10.1 DataFax Overview

DataFax is the data management system used by SCHARP to receive and manage data collected at study sites. The site faxes an electronic image of each case report form (CRF) to SCHARP DataFax, and the original hard copy CRF is retained by the site.

CRF Transmission

Case report forms can be transmitted to SCHARP in one of two ways: faxed using a fax machine connected to the internet (fax to e-mail <datafax@scharp.org>), or if needed a fax machine connected to a land phone line (fax to phone number 206.667.4805).

SCHARP's Information Systems Technology (IST) group is available to consult with the site to determine the best method for data transmission. The SCHARP IST group can be contacted via e-mail at support@scharp.org. The SCHARP IST group should also be contacted anytime the site has technical questions or problems with their fax equipment.

Data Entry/Quality Control

Once a CRF image is received by SCHARP DataFax, the following occurs:

- DataFax identifies the study to which each CRF belongs using the barcode at the top of the form. It reads and enters the data into the study database and stores each CRF on a computer disk.

- 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 refax updated CRF pages to SCHARP DataFax **any time** a change is made to a CRF, regardless of whether or not the change was made in response to a QC report.

10.2 DataFax Form Completion

10.2.1 Guidelines

Based on the use of fax technology and Good Clinical Practices (GCPs), the following guidelines should be used for completing DataFax CRFs:

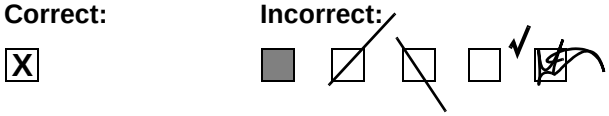
- Use a black or dark blue medium ballpoint pen. Do not use any other type of writing tool. Use only one color per form. That is, do not begin completing a form using a blue pen and then switch to a black pen during the same form completion session.
- Press firmly when recording data or writing comments.
- Print all data and comments legibly by hand. Entries that cannot be read will result in QC notes.
- Do not type data onto CRFs. Do not use cursive/script handwriting, as it can be difficult to read.
- Write numbers as large as possible while staying within the boundaries of the boxes.
- Record data on the front of CRFs only. DataFax cannot read the back of CRFs.
- Do not record data or make marks in the 0.5-inch/1.5-cm margins at the top, bottom, or sides of the CRF.
- If the lines provided for written responses are not long enough, continue in another blank area of the form (within the page margins).
- Mark only one answer except when given the instruction "Mark all that apply."
- A response is required for every item unless instructed otherwise by a skip pattern.
- **Never** obscure, mark over, or punch holes through the barcode at the top of each CRF. DataFax requires the barcode to identify the CRF.
- **Never** use correction fluid ("white-out") or correction tape on CRFs.

- Remove any paper clips, staples, or other attachments before faxing CRFs.
- The site staff person who initially completes the form **must** record his/her initials **and** the date in the space provided in the bottom right-hand corner of each CRF page.
- Fax forms as soon as possible after they have been completed and reviewed. Ideally, completed forms will be faxed to SCHARP within 1–2 days of completing the visit, though up to 5 days is allowed.

10.2.2 How to Mark Response Boxes

Many items on DataFax CRFs have a box or series of boxes for recording a response. Mark the box clearly with an **X**. Do not fill in the box with shading or mark it with a slash or other character.

Correct: **Incorrect:**



Mark only one response box for each item unless the “Mark all that apply” instruction is present.

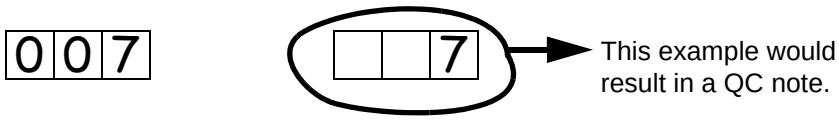
10.2.3 How to Record Numbers

Some questions on DataFax CRFs include boxes for recording a numeric response. DataFax can only read the numbers in these boxes if they are recorded clearly. The following instructions should be followed when recording numeric responses:

- Right justify **all** numbers and fill in any blank leading boxes with zeroes. If boxes are left blank, a QC note will be applied asking for the boxes to be filled in.

  The following example shows how a value of 7 is recorded when three response boxes are provided:

Correct: **Incorrect:**



- Write the number(s) as large as possible while staying within the boundaries of the box; try not to stray outside the boundaries of the box.

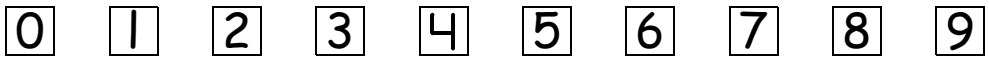
  In the following example, the 4 could be misinterpreted as a 7 or a 1 because DataFax can only read what is *inside* the box:

Correct: **Incorrect:**

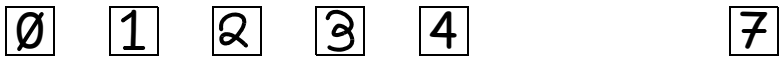
- Write the number(s) simply, with few loops.

The following example shows the format in which numbers will be most easily read by DataFax. Also included are some commonly used formats that may be difficult for DataFax to identify.

Easily Identified:



Difficult to Identify:



10.2.4 How to Record Dates

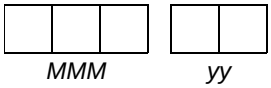
Dates are recorded using the “dd MMM yy” format, where “dd” represents the two-digit day, “MMM” represents the three-letter abbreviation of the month (in capital letters), and “yy” represents the last two digits of the year.

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:

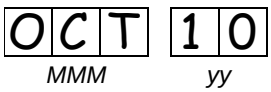
Month	Abbreviation	Month	Abbreviation
January	**JAN**	July	**JUL**
February	**FEB**	August	**AUG**
March	**MAR**	September	**SEP**
April	**APR**	October	**OCT**
May	**MAY**	November	**NOV**
June	**JUN**	December	**DEC**

For example, June 6, 2011 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:

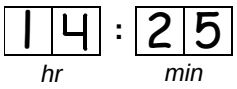


A diagnosis date of October, 2010 would be recorded as follows:



10.2.5 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:

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

10.2.6 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.

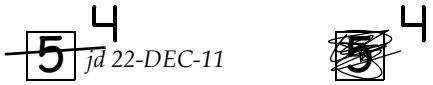
Note: If a correction or addition is made to one page of a multiple-page CRF, only refax the page that was changed.

Note: Never write over an entry once it is recorded. Use the standards outlined in the following paragraphs when changing, clarifying, or amending data.

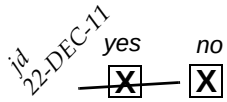
Whenever an entry on a DataFax CRF is changed, do the following:

- 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 as shown below:

Correct: **Incorrect:**

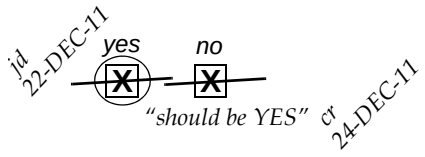


- If an **X** is marked in the wrong response box, correct it by doing the following:
- draw a single horizontal line through the incorrectly marked box,
- mark the correct box, and
- initial and date the correction as shown below:



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:

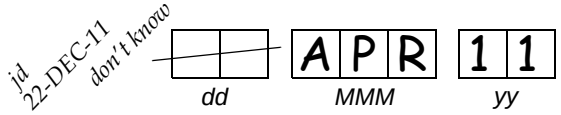


The standards above must ***always*** be followed whenever a CRF is changed, clarified, or amended, even if the change is made ***before*** the CRF is faxed to SCHARP for the first time.

10.2.7 How to Handle Missing and Unknown Data

If the answer to an item is not known, is not available, or if the participant refuses to answer, draw a single horizontal line through the blank boxes and initial and date the item. It is helpful to write "don't know," "refuses to answer," "UNK" (unknown), "N/A" (not applicable), or "REF" (refused) near the blank boxes.

For example, when recording a date, if the exact day is not known, draw a single horizontal line through the "dd" boxes and write "don't know" next to the response boxes, as shown below:



A skip pattern is the **only** valid reason to leave a response blank. Initials and date are required for any data item that is refused, missing, unknown, or not applicable, regardless of whether it is marked as such during the initial form completion, or as an update to the form.

10.3 MTN-012/IPM 010 Study-Specific Data Collection Information

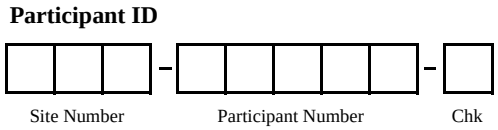
10.3.1 Participant IDs (PTIDs)

DataFax uses a unique participant identification number (PTID) to identify each study participant in the database. SCHARP provides each site with a list of PTIDs prior to study start-up. The site should assign one PTID to each participant enrolled in the study. The PTIDs are assigned in sequential order as participants enroll in the study. The site should ensure that each PTID is assigned only once. Once a participant has received a PTID, he maintains that same PTID throughout the entire study.

PTID boxes are located near the upper left corner of each CRF page.

Site staff are responsible for maintaining a log linking PTIDs to participant names (PTID-Name Link log) in accordance with Section 4 of this manual.

The PTIDs used for this study are nine digits and formatted as “XXX-YYYYY-Z.” The PTID consists of three parts: the DataFax 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-012/IPM 010.



10.3.2 Study Visit Timing

Screening and Enrollment

The initial screening visit is defined as the day the participant provided written informed consent to be screened for the study. The enrollment visit will be scheduled to take place within 30 days of the initial screening visit.

A participant is considered enrolled once the participant has been assigned the appropriate MTN-012/IPM 010 Randomization Envelope (circumcised or uncircumcised). Assignment of MTN-012/IPM 010 Randomization Envelopes will be documented using the appropriate MTN-012/IPM 010 Randomization Envelope Tracking Record provided to each site by SCHARP.

Multiple Screening Attempts (Re-screens)

If a participant’s first screening attempt is unsuccessful, he may re-screen for the study if he chooses. If he does re-screen, 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, that PTID is used for that participant for all re-screening attempts. If a participant re-screens, only case report forms from the successful screening and

enrollment visit are faxed to SCHARP.

Follow-Up Visits

There is 1 required follow-up visit for MTN-012/IPM 010. The visit type, visit code, target visit day, and visit window are listed in Table 10-1. The target days and windows are listed in days, with the day of Enrollment Day 0.

Table 10-1: MTN-012/IPM 010 List of Visits, Visit Codes, Target Visit Dates, and Target Visit Windows

All visit windows are in days; Enrollment = Day 0

Visit	Visit Code	Day Target Window Opens	Target Date	Day Target Window Closes
Screening	01.0	Day -30	**N/A**	Day 0
Enrollment	02.0	N/A	**Day 0**	n/a
Final Clinic Visit	03.0	within 24 hours after last study product application	**Day 7**	Day 14

Target Dates and Visit Windows

All attempts must be made to schedule and complete visits on the target date for the visit. Visit target dates are set based on the enrollment date (Day 0) and do not change if subsequent actual visits take place before or after the target date. Visits completed within the target window will appear on the MTN-012/IPM 010 Retention Reports as being completed “on-time.”

The Final Clinic visit should be targeted to occur within 24 hours of the final study product application. However, there may be cases where it is not possible to complete the visit on the target date. Therefore, the follow up visit may be completed within a visit window around the target date. The visit window for the Final Clinic Visit is +7 days from the target date. For example, if a participant enrolls into MTN-012/IPM 010 on 16 May 2011, his Final Clinic Visit target date is 23 May 2011. However, if he is unable to come to the clinic that day, the Final Clinic Visit can be completed between 23 May 2011 and 30 May 2011. For participants who do not complete scheduled visits within the target window, the visit will be considered “missed” and relevant CRFs will be completed to document the missed visit.

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 the participant’s enrollment date be entered. Once the enrollment date is entered, the target date and visit window for the follow-up visit will appear in the spreadsheet, which can then be printed and added to the participant’s study notebook.

Missed Visits

In those 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, a participant who enrolls into MTN-012/IPM 010 on 22 April 2011 cannot be reached for his Final Clinic Visit within the acceptable visit window (29 April 2011 - 6 May 2011). In this case, since the visit window for that

participant's Final Clinic Visit has "closed," the visit is considered missed, and is documented by completing a Missed Visit form.

Interim Visits

A study visit is considered an interim visit when a participant completes a phone call or presents at the site for additional clinical/laboratory assessments and/or procedures *outside* of the required evaluations for a scheduled study visit. Interim visits may be performed at any time during the study for any reason such as: administrative reasons (a participant has study-related questions for the staff), product-related (a participant needs replacement study product), lab-related (a participant needs a lab test repeated for confirmation), or clinical follow-up (a participant needs additional clinical follow-up for an Adverse Experience). If any data are required to be reported on a DataFax CRF as a result of an interim contact/visit, an Interim Visit form must be completed and faxed to SCHARP DataFax. If no DataFax forms are required for the interim visit (for example, the participant does not report any new AEs during the follow-up phone call), the interim visit may be documented by a chart note only (no CRFs required).

An example of when an Interim visit form would be needed follows:

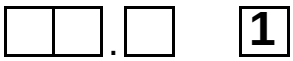
- a participant completes the follow-up phone call as scheduled. During the phone call he reports that he notices slight redness without irritation on his penis where he has been applying the study product. In this case data will be recorded on a DataFax form (i.e. Adverse Experience Log form), This is considered an interim visit and an Interim Visit form is completed to document the visit. Visit code assignment for interim visits is covered in Section 10.3.3. In this case additional interim visits may occur as a result of clinical follow-up.

For questions about phone contacts and assignment of visit codes to such contacts, please contact the SCHARP MTN-012/IPM 010 Project Manager.

10.3.3 Visit Codes, and Page Numbers

Visit Codes

Some DataFax CRFs will include boxes in the upper right corner for a visit code and have the following visit code structure:



Visit Code

DataFax uses the visit code to identify the visit at which a CRF is completed. However, not all DataFax CRFs include boxes for visit codes. If a form is only completed once during a study (for example, the Enrollment form or the Termination 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 given participant and visit. Please see Table 10-1 for specific visit codes used for the study visits.

Visit Codes for Interim Visits

In addition to the scheduled, protocol-required visits listed in Table 10-1, interim visits may occur once the participant is enrolled (see Section 10.2.9 for a definition and examples of unscheduled/ interim visits). Interim visit codes are assigned using the following guidelines:

- In the box to the left of the decimal point, record the one-digit visit code for the most recent scheduled visit (whether that visit was completed or missed).
- Use the guide below to complete the box to the right of the decimal point:
  - ##.1 = the first interim visit after the most recent scheduled visit,
  - ##.2 = the second interim visit after the most recent scheduled visit, and so on.

Example: A participant returns to the site clinic on Day 4 to report new symptoms which require a new AE Log form to be completed. This current visit is considered and interim visit and is assigned the following interim visit code:

Visit Code for this Interim Visit:

Visit Code 0 4 . 1

NOTE: Not all interim visits are assigned 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 form or Product Hold/Discontinuation 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 (i.e., Adverse Experience Log form, Concomitant Medications Log form, Product Hold./Discontinuation Log form), include boxes in the upper-right corner for recording page numbers, as shown below:

Page ☐☐

Assign page numbers in sequential order, starting with 01 (or 001 for Adverse Experience Log forms). For example, the second Concomitant Medications Log page would be assigned page number 02, the third page would be assigned 03, and so on throughout study participation.

10.3.4 Staff Initials/Date

Most CRFs include a line in the lower-right corner for a staff member's initials and the date on which the form was completed. When more than one staff member records data on a CRF, the site should designate the staff member who has primary responsibility for the form. This individual completes the staff initials/date field. The individual not identified in the staff initials/ date field writes his/her initials and date next to each data element for which he/she is responsible.

10.3.5 Case Report Form Completion Schedule

The SCHARP-provided case report forms for this study include DataFax forms (forms that are completed and faxed to SCHARP DataFax) and non-DataFax forms (forms that are completed but **not** faxed to SCHARP DataFax).

Some SCHARP-provided forms are required to be completed at each visit, while other forms are required only at one visit or only when specifically indicated. The following tables (Table 10-2)

lists the DataFax and non-DataFax forms that are **required** to be completed at each MTN-012/IPM 010 study visit.

Table 10-2: Case Report Form Completion Schedule

Screening Visit (within 28 days prior to Enrollment)		**Visit Code: 01.0**
Form Acronym	**Form Name**	**Plate #**
Required		
DEM-1	Demographics	001
Non-DataFax	Behavioral Eligibility	n/a
Non-DataFax	Enrollment Eligibility	n/a
Non-DataFax	Baseline Medical History (from website)	n/a
Non-DataFax	Physical Exam	n/a
GE-1, GE-2	Genital Exam	201, 202
STI-1	STI Laboratory Results	131
LR-1, LR-2	Laboratory Results	135, 136
CM-1	Concomitant Medications Log	423
Enrollment Visit (Day 0)		**Visit Code: 02.0**
Form Acronym	**Form Name**	**Plate #**
Required		
ENR-1, ENR-2	Enrollment	070, 071
PRE-1	Pre-existing Conditions	012
Non-DataFax	Behavioral Eligibility	n/a
Non-DataFax	Physical Exam	n/a
GE-1, GE-2	Genital Exam	201, 202
Non-DataFax	MTN-012/IPM 010 LDMS Specimen Tracking Sheet	n/a
As Needed		
CM-1	Concomitant Medications Log	423
Non-DataFax	Baseline Medical History (from website)	n/a
HTR-1	HIV Test Results	351
Final Clinic Visit		**Visit Code: 03.0**
Form Acronym	**Form Name**	**Plate #**
Required		
FCV-1	Final Clinic Visit	210
Non-DataFax	Follow-up Medical History Log	n/a
Non-DataFax	Physical Exam	n/a
GE-1, GE-2	Genital Exam	201, 202
LR-1, LR-2	Laboratory Results	135, 136
Non-DataFax	MTN-012/IPM 010 LDMS Specimen Tracking Sheet	n/a
SPR-1	Study Product Returns	415
ESI-1	End of Study Inventory	489
TM-1	Termination	490
As Needed		
CM-1	Concomitant Medications Log	423
AE-1	Adverse Experience Log	460
HTR-1	HIV Test Results	351
MV-1	Missed Visit	463

10.3.6 Site Review of DataFax Forms

Each form must be reviewed for completeness and legibility before being faxed to SCHARP DataFax. As part of the review, the site should check the following:

- Other than the participant ID number (PTID), there is no information on the form that could identify the participant (e.g., name, phone number, national identification number, or any other personal identifiers).
- A response has been recorded for each item, unless the item was skipped as instructed by a skip pattern or the item was marked as missing or unknown as described in 10.2.7.
- All text responses are clearly recorded.
- There are no marks on or above the DataFax barcode at the top of each DataFax page.
- There are no:
  - missing dates,
  - missing visit codes,
  - incorrect PTIDs,
  - incorrect visit codes,
  - missing data for items beginning a series of skip patterns, and/or
  - inconsistent or discrepant data.

While CRFs are being reviewed, it is important that they are stored and tracked systematically. It is also necessary to have a system to identify whether a CRF has been faxed to SCHARP DataFax. Such a system may include using a stamp to date the back of the CRF, or utilizing the SCHARP CRF Tracking System (see SSP Section 10.3.7 for more information).

Important: If a date stamp is used to document when the form is faxed, *only* stamp the back of the CRF, *never* the front. Be sure to date stamp the back of the CRF each time it is faxed, including re-faxes.

10.3.7 Faxing DataFax Forms

To streamline the submission of DataFax forms, the site should identify which staff members will be responsible for faxing forms to SCHARP DataFax and receiving and responding to QC reports.

It is important that the sites fax completed DataFax CRFs to SCHARP within the time period specified in the site's MTN-012/IPM 010 Data Management SOP, and that they respond promptly to requests for clarifications and corrections included in QC reports. Early detection of recurrent problems provides an opportunity to reduce errors and improve data quality.

For sites wishing to confirm the receipt of faxed forms at SCHARP, the CRF Tracking System (CTS) is available. This system generates two types of e-mails listings: 1) the number of form pages received at SCHARP; and 2) which specific forms were received at SCHARP for a given PTID and visit. Please contact the MTN-012/IPM 010 Project Manager if you would like to use the CRF Tracking System or for more information about the CRF Tracking System.

10.3.8 Non-DataFax Forms

MTN-012/IPM 010 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 10.2.8 through 10.2.11 should be applied when completing non-DataFax CRFs.

10.4 Form Supply and Storage

10.4.1 Form and Specimen Label Supply

An initial supply of case report forms needed for the study will be supplied by SCHARP using form visit packets, where the packet contains all of the required CRFs for the visit. For example, the Screening Visit packet will include all of the CRFs listed as required for this visit in the Case Report Form Completion Schedule table (Table 10-2). In addition to form packets for each visit listed in Table 10-2, bulk supplies of “as needed” CRFs will be provided to the site (for example, Adverse Experience Log forms, Concomitant Medications Log forms, etc.). Subsequent supplies of forms will be available for download and printing at each site as needed via the ATLAS website.

SCHARP will also ensure sites have access to specimen labels (printed on-site). Specimen labels should be used for all primary specimen collection containers. Please refer to the Laboratory section of the manual for more information on laboratory specimen collection and labeling.

10.4.2 Form Storage

Specifications for form storage will be detailed in the site’s MTN-012/IPM 010 Data Management SOP. It is recommended that for each participant, study CRFs be stored in a hard-cover notebook. SCHARP can provide a template for use in creating notebook cover labels and spine labels. SCHARP can also provide a template that can be used to create tab dividers.

It is suggested that Concomitant Medications Log forms, Adverse Experience Log forms, and Product Hold/Discontinuation Log forms be kept in their own tabbed sections within the participant study notebook. This makes page numbering and updating of these forms easier than if these forms are stored by visit within the participant’s study notebook.

10.5 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-012/IPM010 there are two interviewer-administered forms; meaning CRFs containing questions which must be read aloud word-for-word to the participant as printed on the CRF. The CRFs are the non-DataFax Behavioral Eligibility form and the Demographics form. Other forms, such as the non-DataFax Baseline Medical 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. Completion of these forms can instead consist of more of a “discussion” with the participant rather than a structured, verbatim administration of the items.

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 a glass of water or other beverage.
- Introduce yourself, and try to create a rapport (connection) between yourself and the participant to help him feel comfortable during the interview.
- Let the participant know what you will be talking to him about personal and sensitive topics as part of the visit.

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 know that you are listening and are aware that you are asking him difficult questions. Avoid apologizing for questions or making facial gestures that may show you feel any way but neutral about a question or the participant's response. If the participant feels judged for his behavior, he 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 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 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 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 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 nonjudgmental.
- **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 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 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 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 feel like you don't trust his answers, be aware of whether he is giving you non-verbal cues that indicate he 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 may 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.

10.6 Form Completion Instructions

Detailed form completion instructions for each form are provided on the back of each form page. These instructions include the purpose of each form as well as how each form should be completed. Some items on forms are straightforward and do not require specific instructions. Therefore, not all form items are listed in the forms instructions, and will only see instructions for those items requiring detailed explanation.

Below are some additional instructions for the Pre-existing Conditions, Concomitant Medications Log, Adverse Experience Log, and Laboratory Results forms.

Pre-existing Conditions and Concomitant Medication Log forms:

- For the Pre-existing Conditions and Concomitant Medication Log forms, note that each page must be faxed to SCHARP any time a new entry is added or modified, even if the page is not complete. Do NOT wait to fax to SCHARP until all entries on a page are completed.

Adverse Experience Log (AE Log) form:

- For the Adverse Experience Log form, do not wait until the AE resolves before faxing the form to SCHARP.
- Always make changes, corrections, and updates to the originally-completed Adverse Experience Log form page. Once an AE Log form page has been started and faxed to SCHARP, the data from that page should never be transcribed onto another AE Log form page.

For item 1, note that planned procedures or surgeries are not AEs. For example, a tonsillectomy is not an AE; rather, it is a treatment that will be collected in item 7 of the form. Any adverse experiences associated with the planned procedure or surgery are AEs.

Laboratory Results 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.

10.7 Case Report Forms

This section contains each MTN-012/IPM 010 case report form developed for the study. They are presented in alphabetical order, with the DataFax forms first, followed by the non-DataFax forms. Detailed form completion instructions for each form are provided on the back of each form page.

SAMPLE: DO NOT FAX TO DATAFAX

MTN 012/IPM 010 (187) DEM-1 (001)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number Participant Number Chk

Demographics

Visit Date

[ ][ ] [ ][ ][ ] [ ][ ]

dd *MMM* *yy*

1. What is your date of birth?..... [ ][ ] [ ][ ][ ] [ ][ ] → If unknown, record age: [ ][ ] *years*

dd *MMM* *yy*

male *female*

2. What is your gender? ..... [X] [ ]

NOT APPLICABLE FOR THIS PROTOCOL.

yes *no*

3. Do you consider yourself to be Latino or of Hispanic origin? [ ] [ ]

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 form is used to document participant demographic information.

General Information/Instructions: This form is completed only once for each study participant, at the Screening Visit.

- **Visit Code:** There is no visit code field on this form since this form is only completed once at the Screening Visit.

Item-specific Instructions:

- **Item 1:** If any portion of the date of birth is unknown, record age at time of enrollment. If age is unknown, record participant's estimate of his age. Do not complete both answers.
- **Item 2:** This item does not require a response. This item (gender) has been hard-coded as "male" for all study participants.
- **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.

SAMPLE: DO NOT FAX TO DATAFAX

MTN 012/IPM 010 (187) 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. Randomization envelope number: ..... ___

   4a. Date assigned: ..... __ ___ __ (*dd* *MMM* *yy*)

   4b. Time assigned: ..... __ : __ *24-hour clock* (*hr* *min*)

   4c. Randomization code: ..... ___

5. Date product dispensed by pharmacy: ..... __ ___ __ (*dd* *MMM* *yy*)

6. Is this participant circumcised or uncircumcised? ..... *circumcised* ☐ *uncircumcised* ☐

Comments: _____

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 is assigned a 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 lab specimens stored for future research testing.
- **Item 3a:** Record a complete date.
- **Item 4:** Record the 3-digit envelope number present on the randomization envelope assigned to this participant.
- **Item 4a:** Record the date the randomization envelope was assigned to the participant. This date should match the "date assigned" recorded for this envelope on the MTN-012/IPM 010 Randomization Envelope Tracking Record.
- **Item 4b:** Record the time the randomization envelope was assigned to the participant. Use a 24-hour clock to record time. For example, if the 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-012/IPM 010 Randomization Envelope Tracking Record.
- **Item 4c:** Record the participant's randomization code present on the prescription.
- **Item 5:** Record the exact day, month, and year study product was dispensed to this participant.
- **Item 6:** This item is based on results from the Genital Exam. It is not based on participant self-report.

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number | Participant Number | Chk

Enrollment

7. Did the participant complete the CASI Baseline Behavioral Questionnaire at this visit? .... yes ☐ no ☐ → ***If no, specify in Comments, and go to item 8.***

   7a. Date CASI Baseline Behavioral Questionnaire was completed: .... ☐☐ ☐☐☐ ☐☐ *dd MMM yy*

SPECIMEN STORAGE

Specimen Collection Date

dd *MMM* *yy*

☐☐ ☐☐☐ ☐☐ 8. Plasma .... *stored* ☐ *not stored* ☐ → *Reason:* ____________________

Comments: ____

____

Enrollment (ENR-2)

Item-specific Instructions:

- **Item 7:** Completion of the CASI Baseline Behavioral Questionnaire is required for all participants at the Enrollment Visit. If the required questionnaire was not done, specify the reason on the Comments lines.
- **Item 8:** Record the date that the specimen was *collected* for this visit. A complete date is required.

SAMPLE: DO NOT FAX TO DATAFAX

MTN 012/IPM 010 (187) 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	**Date of Diagnosis/ Surgery** MMM ☐☐☐ yy ☐☐			
Comments	**Severity Grade** ☐ ☐ *not gradable*	**Is condition ongoing?** *yes* ☐ *no* ☐	_____ Staff Initials / Date	

2.

Description	**Date of Diagnosis/ Surgery** MMM ☐☐☐ yy ☐☐			
Comments	**Severity Grade** ☐ ☐ *not gradable*	**Is condition ongoing?** *yes* ☐ *no* ☐	_____ Staff Initials / Date	

3.

Description	**Date of Diagnosis/ Surgery** MMM ☐☐☐ yy ☐☐			
Comments	**Severity Grade** ☐ ☐ *not gradable*	**Is condition ongoing?** *yes* ☐ *no* ☐	_____ Staff Initials / Date	

4.

Description	**Date of Diagnosis/ Surgery** MMM ☐☐☐ yy ☐☐			
Comments	**Severity Grade** ☐ ☐ *not gradable*	**Is condition ongoing?** *yes* ☐ *no* ☐	_____ Staff Initials / Date	

5.

Description	**Date of Diagnosis/ Surgery** MMM ☐☐☐ yy ☐☐			
Comments	**Severity Grade** ☐ ☐ *not gradable*	**Is condition ongoing?** *yes* ☐ *no* ☐	_____ Staff Initials / Date	

6.

Description	**Date of Diagnosis/ Surgery** MMM ☐☐☐ yy ☐☐			
Comments	**Severity Grade** ☐ ☐ *not gradable*	**Is condition ongoing?** *yes* ☐ *no* ☐	_____ 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 Procedures (SSPs). Include current medical conditions and any ongoing conditions such as mental illness, alcoholism, drug abuse, and chronic conditions (controlled or not controlled by medication).

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.
- **Severity Grade:** For each condition, grade the severity according to the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences* and the *Male Genital Toxicity Table*. If a condition is not gradable, mark the "not gradable" box.
- **Is condition ongoing?:** Mark "yes" if condition is ongoing at enrollment.
- **Pre-existing Conditions Revisions and Updates:**If a participant recalls a pre-existing condition at a later date, update the form at that time. Refax updated page(s).

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐☐.☐ 1

MTN 012/IPM 010 (187) RPD-1 (082)

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Replacement Product Dispensation

1. Replacement envelope number: ..... ☐☐☐

   1a. Date opened: ..... ☐☐ ☐☐☐ ☐☐
   dd *MMM* *yy*

   1b. Time opened: ..... ☐☐ : ☐☐ *24-hour clock*
   hr *min*

2. Date replacement product dispensed by pharmacy: ..... ☐☐ ☐☐☐ ☐☐
   dd *MMM* *yy*

3. Replacement randomization code dispensed: ..... ☐☐☐

Form completed by: _____ Staff Initials / Date

Form verified by: _____ Staff Initials / Date

Comments: _____

☐☐☐☒ 16-FEB-11

N:\hivnet\forms\MTN_012\forms\m012_repl_prod_disp.fm

01 Language

_____ Staff Initials / Date

Replacement Product Dispensation (RPD-1)

Purpose: This form is used to document when replacement study product is dispensed.

General Information/Instructions: This form is faxed to SCHARP DataFax only if replacement product is dispensed to an enrolled participant.

- **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:** Record the 3-digit envelope number present on the replacement envelope assigned to this participant.
- **Item 1a:** Record the date the replacement envelope was opened. This date should match the "date assigned" recorded for this envelope on the MTN-012/IPM 010 Replacement Envelope Tracking Record
- **Item 1b:** Record the time the replacement envelope was opened. Use a 24-hour clock to record time. For example, if the 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-012/IPM 010 Replacement Envelope Tracking Record.
- **Item 2:** Record the exact day, month, and year replacement study product was dispensed to this participant.
- **Item 3:** Record the participant's replacement randomization code present on the prescription.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐☐.☐ 1

MTN 012/IPM 010 (187) SPR-1 (083)

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: _____

☐☐☐☒ 16-FEB-11

N:\hivnet\forms\MTN_012\forms\m012_study_prod_ret.fm

01 Language

Staff Initials / Date

Study Product Returns (SPR-1)

Purpose: This form is used to document study product returns.

General Information/Instructions: This form should be completed once for each participant after he has completed study treatment or has been permanently discontinued from study product use.

- **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

Visit Code ☐☐.☐ 1

MTN 012/IPM 010 (187) GE-1 (201)

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Genital Exam

Examination Date

☐☐ ☐☐☐ ☐☐

dd *MMM* *yy*

	EXAM	FINDINGS
1.	Foreskin (internal and external)	*N/A (circumcised)* ☐ *normal* ☐ *abnormal* ☐ → ***If abnormal, specify type of finding.*** *Mark all that apply.* ☐ vesiculation ☐ peeling ☐ bullous reaction ☐ erythema (with induration) ☐ ulceration ☐ erythema (without induration) ☐ bruising, petechiae or ecchymoses ☐ other, specify: _____
2.	Penile Shaft	*normal* ☐ *abnormal* ☐ → ***If abnormal, specify type of finding.*** *Mark all that apply.* ☐ vesiculation ☐ peeling ☐ bullous reaction ☐ erythema (with induration) ☐ ulceration ☐ erythema (without induration) ☐ bruising, petechiae or ecchymoses ☐ other, specify: _____
3.	Glans	*normal* ☐ *abnormal* ☐ → ***If abnormal, specify type of finding.*** *Mark all that apply.* ☐ vesiculation ☐ peeling ☐ bullous reaction ☐ erythema (with induration) ☐ ulceration ☐ erythema (without induration) ☐ bruising, petechiae or ecchymoses ☐ other, specify: _____
4.	Urethral Meatus	*normal* ☐ *abnormal* ☐ → ***If abnormal, specify type of finding.*** *Mark all that apply.* ☐ ulceration ☐ erythema (with induration) ☐ edema ☐ erythema (without induration) ☐ discharge ☐ other, specify: _____

Genital Exam (GE-1)

Purpose: This form is used to document the genital exams conducted during Screening, Enrollment, and follow-up.

General Information/Instructions: For abnormal findings identified after enrollment, complete or update an Adverse Experience Log form when applicable.

- **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 1–4:** If an abnormal finding is observed, mark the appropriate finding(s) in the space provided.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐☐.☐ 1

MTN 012/IPM 010 (187) GE-2 (202)

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Genital Exam

	EXAM	FINDINGS
5.	Scrotum	*normal* ☐ *abnormal* ☐ → ***If abnormal, specify type of finding.*** *Mark all that apply.* ☐ vesiculation ☐ peeling ☐ bullous reaction ☐ erythema (with induration) ☐ ulceration ☐ erythema (without induration) ☐ bruising, petechiae or ecchymoses ☐ other, specify: _____
6.	Inguinal Lymph Nodes	*normal* / *enlarged and painless* / *enlarged and painful* 6a. Right ☐ ☐ ☐ 6b. Left ☐ ☐ ☐

Items 7 and 8 are only completed for visits AFTER Enrollment.

7. During this genital exam, was any dried product observed on the penile shaft, glans, urethral meatus, scrotum, or foreskin? *Mark "none observed" or all that apply.*

☐ none observed
☐ penile shaft
☐ glans
☐ urethral meatus
☐ scrotum
☐ foreskin

8. Were any **new** AE Log pages completed for this visit? ..... *yes* ☐ *no* ☐ → ***If no, end of form.***

8a. Record AE Log page number(s):

AE Log page # ☐☐☐ *AE Log page #* ☐☐☐ *AE Log page #* ☐☐☐

Comments: _____

☐☐☐☒ 16-FEB-11

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01 Language

Staff Initials / Date

Genital Exam (GE-2)

Item-specific Instructions:

- **Item 5:** If an abnormal finding is observed, mark the appropriate finding(s) in the space provided.
- **Items 7–8:** These items are only completed at follow-up visits. Leave these items blank at Screening and Enrollment.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code . 0 1

MTN 012/IPM 010 (187) FCV-1 (210)

Participant ID

Site Number – Participant Number – Chk

Final Clinic Visit

Visit Date

dd MMM yy

1. Date of final study product application: dd MMM yy

2. Time of final study product application: hr : min *24-hour clock*

3. Date of PK blood draw: ..... dd MMM yy **OR** *not done* → ***If not done, record reason(s) on Comments line and go to item 5.***

4. Time of PK blood draw: ..... hr : min *24-hour clock*

5. Did the participant complete the CASI Product Acceptability and Adherence Questionnaire? ..... *yes* *no* → ***If no, end of form.***

   5a. Date CASI Product Acceptability and Adherence was completed: ..... dd MMM yy

Comments: _____

_____

☐ ☐ ☐ ☒ 16-FEB-11

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0 1 Language

Staff Initials / Date

Final Clinic Visit (FCV-1)

Purpose: This form is used to document the required follow-up visit. It is completed at the Final Clinic Visit.

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:** Record a complete date.
- **Item 2:** Use a 24-hour clock to record time. For example, if the time of final study product application was at 9:24 p.m., record 21:24.
- **Item 3:** Record a complete date or mark the “not done” box.
- **Item 4:** Use a 24-hour clock to record time.
- **Item 5:** Completion of the CASI Product Acceptability and Adherence Questionnaire is required for all participants at the Final Clinic Visit. If the required questionnaire was not done, specify the reason on the Comments lines.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐☐.☐ 1

MTN 012/IPM 010 (187) STI-1 (131)

Participant ID

☐☐☐ – ☐☐☐☐☐ – ☐
Site Number | Participant Number | Chk

STI Laboratory Results

Initial Specimen Collection Date

☐☐ ☐☐☐ ☐☐
dd *MMM* *yy*

Alternate Collection Date (*dd* *MMM* *yy*)

Not done/ Not collected ☐ ☐☐ ☐☐☐ ☐☐

1. HIV

	negative	*positive*	*indeterminate*
1a. HIV EIA	☐	☐	☐

If positive or indeterminate, complete HIV Test Results.

Alternate Collection Date (*dd* *MMM* *yy*)

Not done/ Not collected ☐ ☐☐ ☐☐☐ ☐☐

2. SYPHILIS

	non-reactive	*reactive*
2a. Syphilis screening test	☐	☐

If non-reactive, go to item 3.

2a1. Syphilis titer..... **1:** ☐☐☐☐

	negative	*positive*	*indeterminate*
2b. Syphilis confirmatory test	☐	☐	☐

Alternate Collection Date (*dd* *MMM* *yy*)

Not done/ Not collected

3. Gonorrhea and Chlamydia

	negative	*positive*
☐ ☐☐ ☐☐☐ ☐☐ 3a. *N. gonorrhea* (urine)	☐	☐
☐ ☐☐ ☐☐☐ ☐☐ 3b. *C. trachomatis* (urine)	☐	☐

Comments: _____

☐ ☐ ☐ ☒ 16-FEB-11

01 Language

Staff Initials / Date

STI Laboratory Results (STI-1)

Purpose: This form is used to document STI laboratory results as required or clinically indicated during Screening, Enrollment, and follow-up.

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.
- **Results Reporting:**
  - If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results box(es), provide initials and date, and provide an explanation on the Comments line.
- **Repeat Local Laboratory Tests:** Sometimes it is necessary to repeat a local lab test.
  - For a repeat test of the ***same*** **sample**, record only the results considered the most accurate. If a first result was already recorded and faxed to SCHARP DataFax, but the second result is considered more accurate, amend the form to reflect the second result by drawing a line through the first result and writing the second result on the form. Initial and date the change, and refax the amended form to SCHARP DataFax.
  - For a repeat test using a ***different sample*** (e.g., a blood re-draw for a repeat CBC), at Screening or Enrollment, record the repeat test results on the original form by updating the item. Amend the original form to reflect the second result by drawing a line through the first result and writing the second result on the form. Initial and date the change, and refax the amended form to SCHARP DataFax.
  - For a repeat test using a ***different sample*** (e.g., a blood re-draw for a repeat CBC), at follow-up, record the repeat test results on a new form. If the new sample is collected at an unscheduled visit, use an interim visit code. If the new sample is collected at a future scheduled study visit, use that scheduled study visit code. Fax the new form to SCHARP DataFax.

Item-specific instructions:

- **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 was collected after the Initial Specimen Collection Date for this same visit. A specimen collected for the same visit but on a different day should be recorded on the same form only when obtained within the same visit window. A complete date is required.
- **Not done/Not collected:** If the “Not done/Not collected” box is marked, provide an explanation on the Comments lines.
- **Item 1a:** If the HIV EIA result is positive or indeterminate at screening, enrollment, or follow-up, follow the protocol HIV testing algorithm and record the associated test results on the HIV Test Results form.
- **Item 2a1:** Use leading zeros when recording a syphilis titer level. For example, a titer level of 1:32 would be recorded on the form as “1:0032.”

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐☐.☐ 1

MTN 012/IPM 010 (187) LR-1 (135)

Participant ID ☐☐☐-☐☐☐☐☐-☐ (Site Number – Participant Number – Chk)

Laboratory Results

Initial Specimen Collection Date ☐☐ dd ☐☐☐ MMM ☐☐ yy

Alternate Collection Date dd MMM yy

Not done/ Not collected ☐

1. HEMOGRAM

	Not reported			Severity Grade *If applicable*	AE Log Page #	Not reportable as an AE
1a. Hemoglobin	☐	☐☐.☐	g/dL	☐	☐☐☐	OR ☐
1b. Hematocrit	☐	☐☐.☐	%			
1c. MCV	☐	☐☐☐.☐	fL			
1d. Platelets	☐	☐☐☐☐.☐	$x10^3/mm^3$	☐	☐☐☐	OR ☐
1e. WBC	☐	☐☐☐.☐	$x10^3/mm^3$	☐	☐☐☐	OR ☐

Not done ☐ → ***If not done, go to item 2.***

DIFFERENTIAL

	Not reported	Absolute Count *cells/mm3*	Severity Grade *If applicable*	AE Log Page #	Not reportable as an AE
1f. Neutrophils	☐	☐☐☐☐☐	☐	☐☐☐	OR ☐
1g. Lymphocytes	☐	☐☐☐☐	☐	☐☐☐	OR ☐
1h. Monocytes	☐	☐☐☐☐			
1i. Eosinophils	☐	☐☐☐☐			
1j. Basophils	☐	☐☐☐☐			

Comments: _____

☐ ☐ ☐ ☒ 16-FEB-11

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01 Language

Staff Initials / Date

Laboratory Results (LR-1)

Purpose: To document safety laboratory results as required or clinically indicated during screening, enrollment, and follow-up.

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. A complete date is required.

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. A complete date is required.

Results Reporting

- If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results box(es), provide initials and date, and write an explanation on the Comments lines.
- If the site lab does not produce test results in the units used on this form, the results must be converted before the laboratory CRF is faxed to SCHARP. Refer to Study Specific Procedures (SSP) for conversion instructions.
- 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 appropriate *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, record the grade in the appropriate box next to the results.
- Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).
- When working with calculated severity grade ranges (e.g., 1.1–1.5 times the site lab upper limit of normal), the calculated range may have more significant digits than the lab result.
    - Treat all missing digits in the lab value as zeros.
    - If the lab value falls between two calculated severity grade ranges, assign it the higher grade.
- There may be situations in which a lab value falls within a site's lab normal ranges and also within a gradable range per the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*. Per the protocol-specific AE reporting requirements, report this as an AE, as appropriate, and grade it according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*.

AE Log Page #: If the lab value is reportable as an AE, record the page number of the AE Log which is most closely associated with the abnormal lab value.

Not Reportable as an AE: Only mark this box if the lab value is gradable per the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, but is not reportable as an AE. This includes Pre-existing Conditions and abnormal lab values that do not meet protocol-specific AE reporting requirements.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐☐.☐ 1

MTN 012/IPM 010 (187) LR-2 (136)

Participant ID

☐☐☐-☐☐☐☐☐-☐

Site Number Participant Number Chk

Laboratory Results

Not done/ Not collected	Alternate Collection Date dd	MMM	yy			Severity Grade If applicable	AE Log Page #	Not reportable as an AE
2. CHEMISTRIES					U/L			
☐	☐☐	☐☐☐	☐☐	2a. AST (SGOT)	☐☐☐☐	☐	☐☐☐	OR ☐
☐	☐☐	☐☐☐	☐☐	2b. ALT (SGPT)	☐☐☐☐	☐	☐☐☐	OR ☐
					mg/dL			
☐	☐☐	☐☐☐	☐☐	2c. Creatinine	☐☐.☐	☐	☐☐☐	OR ☐

2c1. Calculated creatinine clearance: ..... ☐☐☐ *mL/mm*

2d. Weight ..... ☐☐☐ *kg*

Not done/ Not collected	Alternate Collection Date dd	MMM	yy
☐	☐☐	☐☐☐	☐☐

3. URINE TESTS

Not done		negative or trace	1+	2+	3+	4+	Severity Grade If applicable	AE Log Page #	Not reportable as an AE
☐	3a. Protein	☐	☐	☐	☐	☐	☐	☐☐☐	OR ☐

		negative	positive
☐	3b. Glucose	☐	☐
☐	3c. Blood	☐	☐
☐	3d. Leukocyte esterase (LE)	☐	☐
☐	3e. Nitrites	☐	☐
☐	3f. Culture	☐	☐

Comments: _____

☐☐☐☒ 16-FEB-11

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01 Language

Staff Initials / Date

Laboratory Results (LR-2)

Item-specific Instructions:

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. A complete date is required.

Results Reporting

- If a specimen was collected but results are not available because the specimen was lost or damaged, line through the results box(es), provide initials and date, and write an explanation on the Comments lines.
- If the site lab does not produce test results in the units used on this form, the results must be converted before the laboratory CRF is faxed to SCHARP. Refer to Study Specific Procedures (SSP) for conversion instructions.
- 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 appropriate *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, record the grade in the appropriate box next to the results.
- Always compare the severity grade range to the value that was recorded on the CRF (not the lab-reported value).
- When working with calculated severity grade ranges (e.g., 1.1–1.5 times the site lab upper limit of normal), the calculated range may have more significant digits than the lab result.
    - Treat all missing digits in the lab value as zeros.
    - If the lab value falls between two calculated severity grade ranges, assign it the higher grade.
- There may be situations in which a lab value falls within a site's lab normal ranges and also within a gradable range per the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*. Per the protocol-specific AE reporting requirements, report this as an AE, as appropriate, and grade it according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*.

AE Log Page #: If the lab value is reportable as an AE, record the page number of the AE Log which is most closely associated with the abnormal lab value.

Not Reportable as an AE: Only mark this box if the lab value is gradable per the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, but is not reportable as an AE. This includes Pre-existing Conditions and abnormal lab values that do not meet protocol-specific AE reporting requirements.

- **Item 2c1:** When calculating the participant's creatinine clearance, use the age and weight of the participant at the time the blood specimen is drawn. If the participant was not weighed at the visit when the blood specimen was drawn, but was weighed at a previous visit (within the allowable window for creatinine clearance per the SSP Manual), record the weight from the previous visit. Also, record in the "Alternative Collection Date" boxes the date of the previous visit when the participant was weighed. If the participant has a creatinine value but cannot have his creatinine clearance calculated (due to missing weight data), line through the response boxes and initial and date.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐☐.☐ 1

MTN 012/IPM 010 (187) IV-1 (350)

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
- ☐ 1b. phone call with participant to report new symptoms → ***Complete/Update Adverse Experience Log if applicable.***
- ☐ 1c. follow-up of symptoms and/or AE(s)
- ☐ 1d. participant needs replacement product → ***Complete Replacement Product Dispensation.***
- ☐ 1e. participant is returning used or unused applicators → ***Complete/Update Study Product Returns.***
- ☐ 1f. other, specify: _____

2. Besides this Interim Visit form, what other DataFax study forms were completed at this visit? *Mark all that apply.*

- ☐ 2a. none → ***End of form.***
- ☐ 2b. Genital Exam
- ☐ 2c. Adverse Experience Log (new)

# of pages

2c1. How many **new** AE Log pages have been completed for this visit? ☐☐

- ☐ 2d. Laboratory Results
- ☐ 2e. STI Laboratory Results
- ☐ 2f. Study Product Returns
- ☐ 2g. Product Hold/Discontinuation Log (new)
- ☐ 2h. other, specify: _____

Comments: _____

Interim Visit (IV-1)

Purpose: Complete this form when an interim visit occurs during study follow-up. See the Study-specific Procedures Manual for a definition and examples of interim visits that require an Interim Visit form to be completed.

General Information/Instructions: Any other forms completed for this visit must have the same Visit Code as this Interim Visit form.

Item-specific Instructions:

- **Visit Code:** The following guidelines should be used for assigning the interim visit code:
  - Record the one-digit whole number visit code for the most recent scheduled regular visit. For example, if the most recent scheduled regular visit was Enrollment (Visit Code = 02.0), record "02" to the left of the decimal point in the visit code field.
  - Record the number that corresponds to the Interim Visit in the third box (the box to the right of the decimal point):
    - 0X.1 = First Interim Visit after the most recent scheduled regular visit.
    - 0X.2 = Second Interim Visit after the most recent scheduled regular visit.
- **Item 2:** Note that marking a box 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 2c:** 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 2d1. 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 2g:** Mark this box if a new (previously unreported) product hold or discontinuation is reported at this visit.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code ☐☐.☐

1

MTN 012/IPM 010 (187) HTR-1 (351)

Participant ID

☐☐☐ - ☐☐☐☐☐ - ☐

Site Number Participant Number Chk

HIV Test Results

Sample 1

1. HIV Western Blot or IFA

Not done/ Not collected ☐

Specimen Collection Date ☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*)

negative ☐ *positive* ☐ *indeterminate* ☐

If positive at Screening, go to item 4.

If negative or indeterminate, contact MTN Network Lab.

Sample 2

2. HIV EIA

Not done/ Not collected ☐

Specimen Collection Date ☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*)

negative ☐ *positive* ☐ *indeterminate* ☐

If negative, contact MTN Network Lab.

3. 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.

4. Final HIV status: ..... *negative* ☐ *positive* ☐ *other, specify:* _____

If positive at Screening, participant is ineligible.

Comments: _____

☐ ☐ ☐ ☒ 16-FEB-11

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0 1 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 or indeterminate 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 4 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 4:** 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.
- **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

Note: Number pages sequentially (01, 02, 03) for each participant. Page ☐☐

MTN 012/IPM 010 (187) 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? *Mark all that apply.*

   ☐ 2a. participant unable or unwilling to comply with required study procedures

   ☐ 2b. participant may be put at undue risk

   ☐ 2c. participant reports the use of PEP for possible HIV-1 exposure.

   ☐ 2d. adverse experience → *AE Log page #* ☐☐☐ *AE Log page #* ☐☐☐ *AE Log page #* ☐☐☐

   ☐ 2e. 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)* ☐

   4a. Date and visit code when participant was instructed to resume or permanently discontinue study product use: ☐☐ ☐☐☐ ☐☐ visit code ☐☐.☐
   dd *MMM* *yy*

Comments: _____

Product Hold/Discontinuation Log (PH-1)

Purpose: This form is used to document temporary holds and early permanent discontinuations of study product use for participants.

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 his Day 6 Visit. If, at the same study visit, a product hold/discontinuation is initiated for more than one reason, complete a single Product Hold/Discontinuation Log page and mark all applicable reasons.

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 the "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 he is permanently discontinued from study product use. Mark the "yes" box if study staff instructed the participant that he can resume use of study product. If the participant was permanently discontinued from study product use, mark the "no (permanently discontinued)" box.
- **Item 4a:** Record the date and visit code on which the participant was told by a study staff member that he could resume or that he should permanently discontinue study product use.

SAMPLE: DO NOT FAX TO DATAFAX

Note: Number pages sequentially (01, 02, 03) for each participant **Page** ☐☐

MTN 012/IPM 010 (187) 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* ☐ *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* ☐ *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* ☐ *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	

  - Use "other, specify" for alternate dosing schedules.

- **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

Note: Number pages sequentially (001, 002, 003) for each participant. **Page** ☐☐☐

MTN 012/IPM 010 (187) 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 (in English) 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 a worsening of a pre-existing condition?	☐	☐

Comments: _____

_____

_____

☐ ☐ ☐ ☒ 16-FEB-11

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* and the *Male Genital Toxicity Table*.
- **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, only mark "Permanently discontinued" for the AE that contributed to the permanent discontinuation.
  - ***N/A (not applicable):*** Mark if the AE occurred after the participant had completed all administration of the study product, or the study product is held or permanently discontinued for a different AE or other reason, or the AE is Grade 5-death.
- **Item 6:**
  - ***Continuing:*** AE is continuing at the time it is reported.
  - ***Resolved:*** Condition is no longer present, or returned to the pre-enrollment severity/frequency. If a participant is taking a medication to control an AE that arose during study participation, it is not considered resolved.
  - ***Death:*** Mark only if the severity of this AE is Grade 5. Any other AEs continuing at the time of death should be changed to "continuing at end of study participation."
  - ***Severity/frequency increased:*** If an AE increases in severity or frequency after it has been reported on the AE Log, line through the "Continuing" box previously marked and mark "Severity/frequency increased." Record the date of increase in the "Status/Outcome Date." Report the increase in severity or frequency as a new AE. For this new AE, the "Onset Date" will be the date that the severity or frequency increased. 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 *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2*.

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code . 0 1

MTN 012/IPM 010 (187) 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*

Comments: _____

_____

_____

_____

☐ ☐ ☐ ☒ 16-FEB-11

N:\hivnet\forms\MTN_012\forms\m012_std_MV_07jan10.fm

0 1 Language

Staff Initials / Date

Missed Visit (MV-1)

Purpose: Complete this form whenever an enrolled participant misses a required visit according to the visit window outlined in the protocol or Study Specific Procedures (SSP).

General Information/Instructions: If the QC Report indicates that a visit is overdue, confirm that the visit was missed before completing a Missed Visit form. Fax this form when it is determined that a visit has been missed and cannot be completed within the visit window. Record the Visit Code of the visit that was missed. Record the date that the form was completed. This will not necessarily be the date of the missed visit. A complete date is required.

Item-specific Instructions:

- **Item 1:** Record the target date of the visit. A complete date is required.

SAMPLE: DO NOT FAX TO DATAFAX

MTN 012/IPM 010 (187) 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 (AE-1)	*page #* ☐☐☐	**OR**	*no pages submitted* ☐
3b.	Concomitant Medications Log (CM-1)	*page #* ☐☐		
3c.	Pre-existing Conditions (PRE-1)	*page #* ☐☐		
3d.	Product Hold/Discontinuation Log (PH-1)	*page #* ☐☐	**OR**	*no pages submitted* ☐

Comments:_____

☐ ☐ ☐ ☒ 16-FEB-11

N:\hivnet\forms\MTN_012\forms\m012_std_ESI_07jan10.fm

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

MTN 012/IPM 010 (187) 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. **NOT APPLICABLE FOR THIS PROTOCOL.**
- ☐ 2e. participant relocated, no follow-up planned
- ☐ 2f. investigator decision, specify: _____
- ☐ 2g. unable to contact participant
- 2h. **NOT APPLICABLE FOR THIS PROTOCOL.**
- ☐ 2i. inappropriate enrollment → ***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: _____

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.

Item-specific Instructions:

- **Item 1:** A complete date is required.
- **Item 2:** Mark only the primary reason for termination.
  - **Item 2a:** Scheduled exit visit/end of study: Only mark 2a if the participant completes the protocol-defined final visit.
  - **Item 2b1:** At a minimum, the month and year are required.
  - **Item 2l:** Early study closure: Only mark 2l when instructed by SCHARP.
- **Item 3a:** Record the page number of the Adverse Experience Log on which the AE was recorded. In situations where more than one AE is associated with termination, record the AE that most strongly influenced the decision to terminate. 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.**

MTN 012/IPM 010 (187)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number Participant Number Chk

Enrollment Eligibility

Visit Date

[ ][ ] [ ][ ][ ] [ ][ ]

dd *MMM* *yy*

		yes	*no*
1.	At Screening, is the participant at least 18 years of age?	☐	☐
2.	Is the participant able and willing to provide written informed consent to be screened for and take part in the study?	☐	☐
3.	At Screening, is the participant able and willing to provide adequate locator information, as defined in site SOP?	☐	☐
4.	Is the participant able and willing to communicate in written and spoken English?	☐	☐
5.	At Screening, is the participant HIV-uninfected per HIV Testing Algorithm in Appendix II?	☐	☐
6.	Is the participant in general good health, according to clinical judgment of the Investigator of Record or designee?	☐	☐

If any items 1–6 are marked "no," participant is ineligible.

Enrollment Eligibility (non-DataFax) Page 1 of 2

Purpose: This form is used to document the participant's administrative, clinical, and laboratory eligibility for the study at screening and enrollment. 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 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 and transmission procedures.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN 012/IPM 010 (187)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number Participant Number Chk

Enrollment Eligibility

7. Does the participant have any of the following laboratory abnormalities at Screening:

		yes	no
7a.	hemoglobin < 10.0 g/dL?	☐	☐
7b.	platelet count < 100,000/mm^3?	☐	☐
7c.	white blood cell count < 2,000 cells/mm^3?	☐	☐
7d.	alanine transaminase (ALT) and/or aspartate aminotransferase (AST) > 2.5x the site laboratory upper limit of normal (ULN)?	☐	☐
7e.	serum creatinine > 1.3 x the site laboratory ULN?	☐	☐
7f.	calculated creatinine clearance less than 80 mL/min by the Cockcroft-Gault formula for males?	☐	☐

Note: *Otherwise eligible participants with any of the above exclusionary laboratory results may be re-tested. If a participant is re-tested and a non-exclusionary result is documented within 30 days of providing informed consent for Screening, the participant may be enrolled.*

		yes	no
8.	At Screening or Enrollment, is the participant diagnosed with an STI or reproductive tract infection (RTI) requiring treatment, per current Centers for Disease Control and Prevention (CDC) guidelines?	☐	☐
9.	At Screening or Enrollment, does the participant have a clinically apparent Grade 1 or higher genital exam finding (observed by study staff)?	☐	☐
10.	At Screening or Enrollment, does the participant have any Grade 1 or higher genital or urinary symptoms?	☐	☐
11.	At Screening or Enrollment, is the participant diagnosed with phimosis or hypospadias?	☐	☐
12.	At Screening or Enrollment, are penile, scrotal piercing or penile tattoos observed during genital examination?	☐	☐
13.	Does the participant have any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives?	☐	☐

If any items 7–13 are marked "yes," participant is ineligible.

Enrollment Eligibility (non-DataFax) Page 2 of 2

No additional instructions.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN 012/IPM 010 (187)

Participant ID

☐☐☐ – ☐☐☐☐☐ – ☐

Site Number Participant Number Chk

Behavioral Eligibility

Visit Date

☐☐ ☐☐☐ ☐☐

dd *MMM* *yy*

To confirm your eligibility for the study, I need to ask you a few more questions.

		yes	*no*
1.	Are you willing to abstain from the following during study participation:		
1a.	vaginal intercourse, even with a condom?	☐	☐
1b.	oral intercourse, even with a condom?	☐	☐
1c.	anal intercourse (including receptive anal intercourse), even with a condom?	☐	☐
1d.	masturbation and other activities that may cause irritation or injury to the penis?	☐	☐
1e.	using genitally-applied preparations (except use of usual cleansing products for genital hygiene) other than the study product?	☐	☐
1f.	non-urgent surgical procedures of the penis/GU area?	☐	☐
2.	Do you 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 complete)?	☐	☐

If any items 1–2 are marked "no," participant is ineligible.

Behavioral Eligibility (non-DataFax) Page 1 of 2

Purpose: This form is used to document the participant's behavioral eligibility for the study at screening and enrollment. 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 Behavioral 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 and transmission procedures.

General Information/Instructions: If the participant provides a response indicating he is ineligible, continue to administer this form until all items are completed. Refrain from indicating to the participant the reason why he is ineligible.

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN 012/IPM 010 (187)

Participant ID

[ ][ ][ ] – [ ][ ][ ][ ][ ] – [ ]

Site Number | Participant Number | Chk

Behavioral Eligibility

3. Do any of the following apply to you:

		yes	no	N/A
3a.	known adverse reaction to any of the study products or components of the study products (ever)?	☐	☐	
3b.	post-exposure prophylaxis (PEP) for HIV exposure within 6 months prior to Enrollment?	☐	☐	
3c.	penile procedures (e.g., biopsy, circumcision) within 42 days or less prior to Enrollment?	☐	☐	
3d.	participation in any other research studies involving drugs, medical devices, or genital products within 30 days prior to Enrollment?	☐	☐	
3e.	within 3 months prior to Enrollment, history of a non-gonococcal urethritis and/or sexually transmitted infection (STI), including outbreak of genital herpes or condylomata?	☐	☐	
3f.	for uncircumcised men, the treatment of candidal balanoposthitis/balanitis within 30 days prior to Enrollment?	☐	☐	☐
3g.	history of recurrent dermatosis (e.g., eczema)?	☐	☐	
3h.	non-therapeutic injection drug use within 12 months or less prior to Screening?	☐	☐	
3i.	currently using an immunosuppressant (with the exception of local non-genital use of low potency products e.g., inhaled corticosteroid for asthma)?	☐	☐	

If "yes," participant is ineligible.

Behavioral Eligibility (non-DataFax) Page 2 of 2

No additional instructions.

SAMPLE: DO NOT FAX TO DATAFAX

Not a DataFax form. Do not fax to DataFax.

MTN 012/IPM 010 (187)

Participant ID

Site Number	Participant Number	Chk

Follow-up Medical History Log

Page ☐☐☐

Medical Condition	Onset Date (dd-MMM-yy)	Staff Initials/Log Entry Date	Is this condition reportable as an AE? yes ☐ no ☐ → AE Log Page # ☐☐☐
	Outcome Date (dd-MMM-yy)	**Severity Grade**	
Comments			**Medication taken?** yes ☐ no ☐ → *Report on Concomitant Medications Log.*

Medical Condition	Onset Date (dd-MMM-yy)	Staff Initials/Log Entry Date	Is this condition reportable as an AE? yes ☐ no ☐ → AE Log Page # ☐☐☐
	Outcome Date (dd-MMM-yy)	**Severity Grade**	
Comments			**Medication taken?** yes ☐ no ☐ → *Report on Concomitant Medications Log.*

Medical Condition	Onset Date (dd-MMM-yy)	Staff Initials/Log Entry Date	Is this condition reportable as an AE? yes ☐ no ☐ → AE Log Page # ☐☐☐
	Outcome Date (dd-MMM-yy)	**Severity Grade**	
Comments			**Medication taken?** yes ☐ no ☐ → *Report on Concomitant Medications Log.*

Medical Condition	Onset Date (dd-MMM-yy)	Staff Initials/Log Entry Date	Is this condition reportable as an AE? yes ☐ no ☐ → AE Log Page # ☐☐☐
	Outcome Date (dd-MMM-yy)	**Severity Grade**	
Comments			**Medication taken?** yes ☐ no ☐ → *Report on Concomitant Medications Log.*

Follow-up Medical History Log

This form is used to document and track **all** medical conditions observed in or reported by the study participant during follow-up. This includes all signs, symptoms, and laboratory-based medical conditions. This form is reviewed and updated at each study visit and participant contact (e.g., telephone contacts), including interim visits/contacts, unless stated otherwise by the protocol.

Item-specific Instructions

- **Page:** Number pages sequentially throughout the study, starting with 001. Do not repeat page numbers.
- **Medical Condition:** Whenever possible, provide a diagnosis. Include anatomical location when applicable. Record only one diagnosis, sign, or symptom per entry.
- **Onset Date:** Record complete dates whenever possible. At a minimum, month and year are required. If the "day" portion is not known, record zeros for the day (example "00-JAN-11").
- **Outcome Date:** Record a complete date whenever possible. At a minimum, month and year are required. Record the date on which the participant no longer experiences the medical condition or the date of the study visit or specimen collection at which the resolution/status outcome is first noted. If the outcome is not able to be obtained (for example, a participant is lost to follow-up), record "unknown".
- **Severity:** Consult the appropriate *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Experiences* as specified by the protocol.
- **Is this condition reportable as an AE?:** Mark "yes" if the condition has been reported on an AE Log case report form. Refer to the protocol for a listing of which conditions are required to be reported on an AE Log form.

Review Documentation

For every follow-up visit, document that this log page was reviewed (and updated, as applicable) by recording a staff initials and date in one of the spaces below. Note that the page does not need to be reviewed once **all** conditions on the page have a recorded outcome date.

Staff Initials/Date	*Staff Initials/Date*	*Staff Initials/Date*	*Staff Initials/Date*
Staff Initials/Date	*Staff Initials/Date*	*Staff Initials/Date*	*Staff Initials/Date*
Staff Initials/Date	*Staff Initials/Date*	*Staff Initials/Date*	*Staff Initials/Date*
Staff Initials/Date	*Staff Initials/Date*	*Staff Initials/Date*	*Staff Initials/Date*

SAMPLE: DO NOT FAX TO DATAFAX **Not a DataFax form. Do not fax to DataFax.**

MTN 012/IPM 010 (187)

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, then go to item 2.*** *Reason:* _____

1a. Oral Temp ..... [ ][ ] . [ ] *°C*

1b. BP ..... [ ][ ][ ] / [ ][ ][ ] *mmHg*

1c. Pulse ..... [ ][ ][ ] *per minute*

_____
Vital Signs: Staff Initials / Date

2. Height: ..... [ ][ ][ ] *cm* ***OR*** [ ] *not done*

FINDINGS

not evaluated	*normal*	*abnormal* → ***If abnormal, please specify.***
[ ]	[ ]	[ ] 3. General appearance _____
[ ]	[ ]	[ ] 4. Abdomen _____
[ ]	[ ]	[ ] 5. HEENT _____
		_____
[ ]	[ ]	[ ] 6. Oral Mucosa _____
[ ]	[ ]	[ ] 7. Neck _____
[ ]	[ ]	[ ] 8. Lymph Nodes _____
[ ]	[ ]	[ ] 9. Heart _____
[ ]	[ ]	[ ] 10. Lungs _____
[ ]	[ ]	[ ] 11. Extremities _____
[ ]	[ ]	[ ] 12. Neurological _____
[ ]	[ ]	[ ] 13. Skin _____

If any are abnormal and ongoing at Enrollment, record findings on Pre-existing Conditions form.
If abnormal during follow-up, update or complete Adverse Experience Log when applicable.

_____
Findings: Staff Initials / Date

Comments: _____

[ ][ ][ ][X] 16-FEB-11

0 1
Language

_____
Staff Initials / Date

Physical Exam

Purpose: This form is used to document the participant's vital signs and physical exam findings.

General Information/Instructions: This form is completed each time a physical exam is performed. Because this is a non-DataFax form, do NOT fax to SCHARP DataFax.

Item-specific Instructions:

- **Vital Signs:** Use leading zeros when needed. The staff member who completes these items should initial and date in the space provided.
- **Findings:** The staff member who completes these items should initial and date in the space provided.

Section 11. Data Communiqués

For MTN-012/IPM 010, 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 a copy in this section of each MTN-012/IPM 010 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-012/IPM 010 Data Communiqué #1

April 5, 2011

This is official study documentation for MTN-012/IPM 010. Please circulate it among relevant staff for their review, print it, and place it in your MTN-012/IPM 010 SSP Manual in the Data Communiqués section.
This document is considered part of the MTN-012/IPM 010 SSP manual.

UPDATES

None.

CLARIFICATIONS

1. **Final Clinic Visit form**

   Visit Code. The Visit code for this form has a "0" pre-printed in the box after the decimal point. In most cases this form will be completed at the scheduled Final Clinic Visit, when the visit code will be 03.0. If for any reason this form is completed at an interim visit (i.e. outside of the visit window for the Final Clinic Visit), please line through the "0," write "1" near the box, and initial and date this change. Be sure to make all marks within the margins of the form.

REMINDERS

None.

Section 12. Behavioral Measures: Web-based Questionnaires

12.1 Types of Behavioral Questionnaires

There will be two sets of behavioral measures collected in MTN-012/IPM 010: the Baseline Behavioral Questionnaire, and the Product Acceptability and Adherence Questionnaire. The Baseline Behavioral Questionnaire will be used to collect information on all participants' sexual behaviors, drug and alcohol use, and knowledge of microbicides, amongst other things. The Product Acceptability and Adherence Questionnaire will be used to collect information on participants' experiences with the gel, their likelihood to use a microbicide in the future and their use of study product. Data collection for the Baseline Behavioral and Product Acceptability and Adherence 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 timing of these questionnaires is listed in Table 12-1.

Table 12-1: Timing of Behavioral Measures

Study Visit	Behavioral Measures
Enrollment Visit	Baseline Behavioral Questionnaire (CASI)
Final Clinic Visit	Product Acceptability and Adherence Questionnaire (CASI)

The purpose of this SSP section is to describe the process for conducting CASI.

12.2 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 and 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 questionnaires 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. Sites should have an anti-virus program installed on the computer used for questionnaires. 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).

For questions regarding general computer problems or issues with administering or accessing the questionnaires, please refer to Section 12.5 in this manual for contact information.

12.3 Administering Behavioral Measures

As mentioned in Table 12-1, the Behavioral Measures that will be collected during the course of the study are:

- Enrollment Visit: Baseline Behavioral Questionnaire
- Final Clinic Visit: Product Acceptability and Adherence Questionnaire

If a participant discontinues trial participation early, he will be encouraged to respond to the Product Acceptability and Adherence Questionnaire at the time he exits the study.

12.3.1 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/MTN012bbq/

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), Study Code (MTN012) and re-entering the PTID (without spaces) for confirmation.
2) Enter the visit code: 2.0.
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.) The staff member should remain with the participant at this point and allow the participant to complete the practice questions, assisting him if needed, to make sure he 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 used the gel 100 times).
7) Let the participant know that he can refuse to answer any question.

   Note: If the participant is unsure of his answer, encourage the participant to make his best guess rather than refuse. Answer any questions that the participant may have and let him know that you are available for help.

8) Instruct the participant to notify staff once he sees a message at the end of the questionnaire indicating that he has completed the questionnaire which states: PLEASE STOP HERE AND TELL INTERVIEWER THAT YOU ARE FINISHED, or if he 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 own. The participant should be the only person in the room at the time he is completing the questionnaire.

10) When the participant calls you after he has finished the questionnaire, enter the password: 2011.

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 12.5 below for guidelines and contact information regarding troubleshooting and problems with administering the questionnaire.

12.3.2 Administering the Product Acceptability and Adherence Questionnaire (Final Clinic Visit)

To begin, access the Web page for the Product Acceptability and Adherence Questionnaire at the following URL:

http://www.scharp.org/MTN012paq/

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) and Study Code (MTN012) and re-entering the PTID (without spaces) for confirmation.

2) Enter the Visit Code. The acceptable range for the Product Acceptability Questionnaire is 2.1-3.0.

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.) The staff member should remain with the participant at this point and allow the participant to complete the practice questions, assisting him if needed, to make sure he 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 used the gel 100 times).

7) Let the participant know that he can refuse to answer any question.

Note: If the participant is unsure of his answer, encourage the participant to make his best guess rather than refuse. Answer any questions that the participant may have and let him know that you are available for help.

8) Instruct the participant to notify staff once he sees a message at the end of the questionnaire indicating that he has completed the questionnaire which states: PLEASE STOP HERE AND TELL THE INTERVIEWER THAT YOU ARE FINISHED, or if he 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 own. The participant should be the only person in the room at the time he is completing the questionnaire.

10) When the participant calls you after he has finished the questionnaire, enter the password: 2011.

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 12.5 below for guidelines and contact information regarding troubleshooting and problems with administering the questionnaire.

12.4 Participants Who Discontinue Study Product

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 should complete the Product Acceptability and Adherence Questionnaire at the Final Clinic Visit.

12.5 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 ***mtn012webtrouble@mtnstopshiv.org***. The team of staff members (Corey Miller and Lynda McVarish at SCHARP; Craig Hoesley at UAB; Ashley Mayo and Lisa Levy at FHI, Penny Shaw at University of Pittsburgh; and Curtis Dolezal and Marina Mabragaña at the HIV Center) will be available to assist you to troubleshoot and resolve any problems you may have with the Web-based questionnaires.

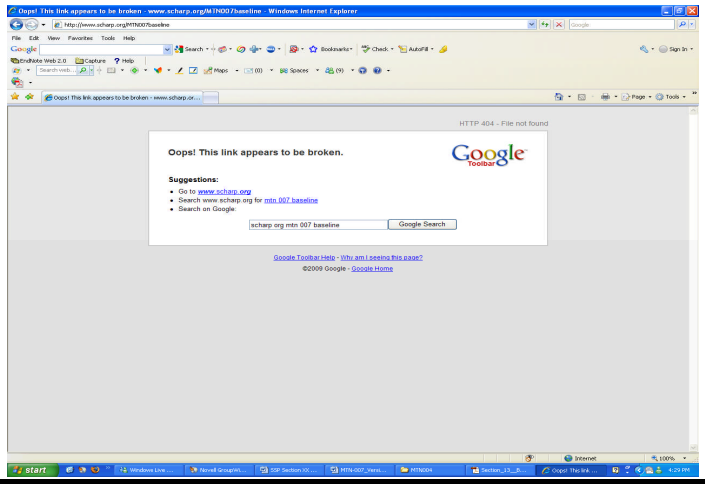
To facilitate the troubleshooting process, please indicate in your email a description of the problem, including a copy of the error message(s), if any, and date and time of when the problem occurred. It is very useful to the MTN-012/IPM 010 Web Trouble team to have an exact copy of error messages. To 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 [insert date].doc and attach it to your email to the MTN-012/IPM 010 Web Trouble team. An example of an email message to the Web Trouble team is presented in Figure 12-1.

Figure 12-1: Email Error Message

To: **mtn012webtrouble@mtnstopshiv.org**
From: XXX
Date: May 16, 2011, 10:28am EST
Re: MTN 012 Web Problem

No access to the Baseline Behavioral Questionnaire on May 16, 2011 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: MTN012WebProblem_5-16-11.doc)]



The following mock PTIDs IDs will be used to troubleshoot any problems and for practice sessions:

MOCK Participant ID's:

Site: Pittsburgh	Site: Alabama
999-30101-7	999-30126-2
999-30102-8	999-30127-3
999-30103-4	999-30128-5
999-30104-2	999-30129-8
999-30105-6	999-30130-1
999-30106-9	999-30131-6
999-30107-5	999-30132-7
999-30108-3	999-30133-0
999-30109-1	999-30134-3
999-30110-9	999-30135-5
999-30111-3	999-30136-8
999-30112-4	999-30137-9
999-30113-8	999-30138-4
999-30114-6	999-30139-2

999-30115-2	999-30140-8
999-30116-0	999-30141-4
999-30117-1	999-30142-0
999-30118-7	999-30143-7
999-30119-5	999-30144-5
999-30120-7	999-30145-3
999-30121-0	999-30146-1
999-30122-1	999-30147-2
999-30123-6	999-30148-6
999-30124-9	999-30149-9
999-30125-4	999-30150-3

Marina Mabragaña will coordinate efforts to quickly resolve any problems. She will keep a record of any problems in a log (MTN-012 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:

- Marina Mabragaña at (212) 568-4237 or mabraga@pi.cpmc.columbia.edu

You may also contact:

- Corey Miller at (206) 667-7672 or corey@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). Then go back using the back arrow until reaching the first question and let the participant start the questionnaire again. If the problem persists, contact mtn012webtrouble@mtnstopshiv.org and call Marina Mabragaña so that actions can be taken immediately. The MTN-012/IPM 010 Web Trouble team will assess the problem and communicate with you about resolutions. 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-012/IPM 010 Web Trouble Log.

Refer to Appendix 12-1 for "Quick Tips for Web-Based Behavioral Questionnaires"
Refer to Appendix 12-2 for the Behavioral Measures Questionnaires

Section Appendix 12-1
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 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/MTN012bbq/

    2. Product Acceptability and Adherence Questionnaire (Final Clinic Visit)
       http://www.scharp.org/MTN012paq/

- 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: MTN012, and enter PTID again to confirm.

- Enter the Visit Code. The acceptable visit code for the Baseline Behavioral Questionnaire is 2.0. The acceptable range for the visit code of the Product Acceptability and Adherence Questionnaire is 2.1-3.0.

- Enter the current date.

- Allow participant to complete the practice questions.

- Assist the participant as needed.

- Instruct the participant that when he reaches the end of the survey, he will see a screen that says "PLEASE STOP HERE AND TELL THE INTERVIEWER THAT YOU ARE FINISHED." The participant is not finished until he reaches this end screen. At that point the participant should leave the computer as is and inform the site staff.

- Enter the password: 2011. 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. Click the back arrow until reaching the first question and let the participant start the questionnaire again.

  If you encounter any problems with the questionnaires or with the laptop/desktop that you are using, notify mtn012webtrouble@mtnstopshiv.org.

Section Appendix 12-2

Behavioral Assessments

Participant ID | | | | |

Date ___/___/_____
MM DD YYYY

MTN-012/IPM 010

Baseline Behavioral Questionnaire

Presentation Version

2-10-11, version 1.3

Ross Cranston, M.D., Protocol Chair

Alex Carballo-Diéguez, Ph.D., Co-Investigator

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 "back" arrow.
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

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? [SKIP TO Q 5L]
_____ 2 Not Hispanic or Latino?
_____ 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 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 Do you consider yourself (check all that apply)…

_____ 1 Straight/heterosexual?
_____ 2 Gay/homosexual?
_____ 3 Bisexual?

_____ 4 Other? (please specify): _____

_____ 5 Refuse to answer

7 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 (please specify): _____

_____ 7 Refuse to answer

8 Please check what describes who you live with now...

_____ 1 You live alone

_____ 2 You live with a partner, spouse, or steady girlfriend/boyfriend

_____ 3 You live with family members, friends, or roommates (not spouse)

_____ 5 You are homeless or do not have a regular place to live now

_____ 6 Other (please 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. SEXUAL BEHAVIOR

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."

Intercourse is when a man puts his penis into a partner's vagina, rectum, or anus. It includes both anal and vaginal intercourse.

Vaginal intercourse is when a man puts his penis into a woman's vagina; some people call this "fucking" or "screwing" or "having sex."

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."

Insertive anal intercourse, or insertive anal sex, is when you put your penis in another man or woman's rectum, or your "dick" in his/her "ass". Some people call this "butt fucking" or "topping".

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".

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 WOMEN

First, you will be asked about your sexual behavior with women.

1. During the past three months, how many female sexual partners have you had?

_____ [IF 0, SKIP QUESTIONS ON SEX WITH WOMEN AND GO TO QUESTIONS ON SEX WITH MEN]

_____ Refuse to answer

1x. You responded Refuse to answer for the previous question. Please confirm:
1. I refuse to answer questions about female sexual partners [IF YES, GO TO QUESTIONS ON SEX WITH MEN]
2. I am willing to answer questions about female sexual partners

Of these women, 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 a spouse or steady girlfriend (a woman with whom you've felt emotionally involved, in a commited relationship, and with whom you had sex)

_____

1A.2 one-night stands (women with whom you had sex only once)

_____

1A.3 other female partners (women with whom you had sex who are neither your spouse, steady girlfriends nor one-night stands)

_____

1AX.1 Refuse to answer

Vaginal Intercourse
In the past three months ...

2. How many times did you put your **penis** in a **vagina**?

_____ [IF 0, GO TO Q 9]

_____ Refuse to answer

3. How many times did you put your **penis** in a **vagina** without a condom?

_____ [IF 0, GO TO Q 9]

_____ Refuse to answer

4. Into how many women's **vagina**s did you put your **penis** without a condom?

_____

_____ Refuse to answer

[CASI, IF Q 4 = 1 (I.E., THE PARTICIPANT REPORTS THAT HE PENETRATED ONLY ONE WOMAN WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 5; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 6]

You said you put your penis in one woman's vagina without a condom.

5. 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 4 IS 2 OR MORE (I.E., THE PARTICIPANT REPORTS THAT HE PENETRATED TWO OR MORE WOMEN WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 6; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 9]

You said you put your penis in ___ women's [CASI CAN INSERT THE NUMBER FROM THE PREVIOUS QUESTION (Q 4)] vaginas without a condom.

6. Of those women, how many had actually told you they were HIV-negative and you had no reasons to doubt it?

_____

7. Of those women, how many do you know to be HIV-positive?

_____

8. How many were you NOT completely sure about their HIV status?

_____

8X.1 Refuse to answer

Anal Intercourse
In the past three months ...

9. How many times did you put your penis in a woman's **rectum**?

_____ [IF 0, GO TO Q 16]

_____ Refuse to answer

10. How many times did you put your penis in a woman's **rectum** without a condom?

_____ [IF 0, GO TO Q 16]

_____ Refuse to answer

11. Into how many women's **rectum**s 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 WOMAN IN THE RECTUM WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 12; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 13]

You said you put your penis in one woman's rectum without a condom.

12. 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 11 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 13; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 16]

You said you put your penis in ____ women's [CASI CAN INSERT THE NUMBER FROM THE PREVIOUS QUESTION (Q 32)] rectums without a condom.

13. Of those women, how many had actually told you they were HIV-negative and you had no reasons to doubt it?

_____

_____ Refuse to answer

14. Of those women, how many do you know to be HIV-positive?

_____

_____ Refuse to answer

15. How many were you NOT completely sure about their HIV status?

_____

15X.1 Refuse to answer

SEXUAL BEHAVIOR WITH MEN

Now you will be asked questions about your sexual behavior with men.

16. During the past three months, how many male sexual partners have you had?

_____ [IF 0, SKIP QUESTIONS, GO TO QUESTION 31.]
_____ Refuse to answer

16x. You responded Refuse to answer for the previous question. Please confirm:
1. I refuse to answer questions about male sexual partners [IF YES, GO TO QUESTION 31]
2. I am willing to answer questions about male sexual partners

Of these men, 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 Q16]):

16A.1 spouse, lover or boyfriend (men with whom you've felt emotionally involved in a committed relationship and with whom you had sex)

_____

16A.2 one-night stands (men with whom you had sex only once)

_____

16A.3 other male partners (men with whom you had sex who are neither your spouse, lover or boyfriend nor one-night stands)

_____

16AX.1 Refuse to answer

Receptive Anal Intercourse
In the past three months ...

17. How many times did a male partner put his **penis** in your **rectum**?

_____ [IF 0, GO TO Q 923]

_____ 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.]

18. How many times did a male partner put his **penis** in your **rectum** without a condom?

_____ [IF 0, GO TO Q 23.]

_____ 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.]

19. How many men put their **penis**es in your **rectum** without a condom?

_____

_____ Refuse to answer

[CASI, IF Q 19 = 1 (i.e., THE PARTICIPANT REPORTS THAT ONLY ONE MAN PENETRATED HIM WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 20; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 21]

You said that one man put his penis in your rectum without a condom.

20. 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 19 IS 2 OR MORE (I.E., THE PARTICIPANT REPORTS THAT TWO OR MORE MEN PENETRATED HIM WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 21; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 24]

You said ___ men [CASI CAN INSERT THE NUMBER FROM THE PREVIOUS QUESTION (Q 19)] put their penises in your rectum without a condom.

21. Of those men, how many had actually told you they were HIV-negative and you had no reasons to doubt it?

_____

22. Of those men, how many do you know to be HIV-positive?

_____

23. How many were you NOT completely sure about their HIV status?

_____

23X.1 Refuse to answer

Insertive Anal Intercourse
In the past three months ...

24. How many times did you put your penis in a man's rectum?

_____ [IF 0, GO TO Q 16]

_____ Refuse to answer

25. 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

26. Into how many men's rectums did you put your penis without a condom?

_____

_____ Refuse to answer

[CASI, IF Q 26 = 1 (I.E., THE PARTICIPANT REPORTS THAT HE PENETRATED ONLY ONE MAN WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 27; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 28]

You said you put your penis in one man's rectum without a condom.

27. 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 26 IS 2 OR MORE (I.E., THE PARTICIPANT REPORTS THAT HE PENETRATED TWO OR MORE MEN WITHOUT A CONDOM), GO TO INSTRUCTIONS ABOVE Q 28; OTHERWISE SKIP TO INSTRUCTIONS ABOVE Q 31]

You said you put your penis in ___ men's [CASI CAN INSERT THE NUMBER FROM THE PREVIOUS QUESTION (Q 11)] rectums without a condom.

28. Of those men, how many had actually told you they were HIV-negative and you had no reasons to doubt it?

_____

29. Of those men, how many do you know to be HIV-positive?

_____

30. How many were you NOT completely sure about their HIV status?

_____

30X.1 Refuse to answer

31. Are you circumcised?
1. No [SKIP TO NEXT SECTION]

2. Yes
3. Refuse to answer

32. Were you circumcised …
1. At birth
2. In childhood or during adolescence
3. During adulthood
4. Refuse to answer

SECTION C. LUBRICANT AND SPERMICIDE USE

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 Have you ever used a commercial sexual lubricant (e.g, Femglide®, ID®, or KY®?

_____ 1 Yes
_____ 2 No [SKIP TO NEXT SECTION]
_____ 3 I don't know [SKIP TO NEXT SECTION]
_____ 4 Refuse to answer

Vaginal Intercourse [IF Q B2 > 0]

2 During the past three months, how frequently have you had **vaginal intercourse** using a commercial sexual lubricant?

_____ 1 Never [ASK Q 3 AND SKIP TO Q 10]
_____ 2 Sometimes [ASK Q 3 AND CONTINUE WITH THIS SECTION]
_____ 3 Always [SKIP Q 3 AND GO TO Q 4]
_____ 4 Refuse to answer

3 During the past three months, when you did NOT use a lubricant for **vaginal intercourse**, why was that the case? [Indicate all that apply] [IF Q 2 = 1, ASK THIS QUESTION AND SKIP TO NEXT SECTION; OTHERWISE GO TO Q 4]

_____ 1 I did not feel it was needed
_____ 2 Sometimes I prefer dry sex
_____ 3 I disliked the lubricant
_____ 4 I used saliva
_____ 5 I used condoms with lubricant
_____ 6 Lubricant was not available
_____ 7 I was in a rush
_____ 8 I couldn't afford to buy it
_____ 9 My partner refused
_____ 10 Other (please specify): _____
_____ 11 Refuse to answer

4 During **vaginal intercourse**, how much commercial lubricant do you use on average?

_____ 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 In terms of commercial lubricant consistency, what do you prefer for vaginal intercourse?

_____ 1 Very liquid
_____ 2 Somewhat liquid
_____ 3 Neither
_____ 4 Somewhat thick
_____ 5 Very thick
_____ 6 Refuse to answer

6 In general when you have vaginal intercourse, is the lubricant applied…[Indicate all that apply]

_____ 1 Directly on your penis?
_____ 2 On the outside of your partner's vagina?
_____ 3 Inside your partner's vagina?
_____ 4 Inside the condom?
_____ 5 On the outside of the condom?
_____ 6 Other (please specify):_____
_____ 7 Refuse to answer

7 When you are having vaginal intercourse, who applies the lubricant?

_____ 1 Self
_____ 2 Partner
_____ 3 Both
_____ 4 Refuse to answer

8 When is the lubricant first applied?

_____ 1 Before there is any sexual contact
_____ 2 During sex but before you penetrate her
_____ 3 After you first penetrate her if you feel the need for it
_____ 4 Refuse to answer

9 How frequently do you usually reapply the commercial lubricant during vaginal intercourse?

_____ 1 Never
_____ 2 Once
_____ 3 Twice
_____ 4 3 times or more
_____ 5 Refuse to answer

[IF Q B9 OR Q B24 > 0] The following questions refer to **insertive anal intercourse** only.

10 During the past three months, how frequently have you used a commercial lubricant during **insertive anal intercourse**?

_____ 1 Never [ASK Q 11 AND SKIP TO Q 18]
_____ 2 Sometimes [ASK Q 11 AND CONTINUE WITH THIS SECTION]
_____ 3 Always [SKIP Q 11 AND GO TO Q 12]

_____ 4 Refuse to answer

11 During the past three months, when you did NOT use a lubricant for **insertive anal intercourse**, why was that the case? [Indicate all that apply] [IF Q 10 = 1, ASK THIS QUESTION AND SKIP TO NEXT SECTION; OTHERWISE GO TO Q 12]

_____ 1 I did not feel it was needed
_____ 2 Sometimes I prefer dry sex
_____ 3 I disliked the lubricant
_____ 4 I used saliva
_____ 5 I used condoms with lubricant
_____ 6 Lubricant was not available
_____ 7 I was in a rush
_____ 8 I couldn't afford to buy it
_____ 9 My partner refused
_____ 10 Other (please specify): _____
_____ 11 Refuse to answer

12 During insertive anal intercourse, how much commercial lubricant do you use on average?

_____ 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

13 In terms of commercial lubricant consistency, what do you prefer for insertive anal intercourse?

_____ 1 Very liquid
_____ 2 Somewhat liquid
_____ 3 Neither
_____ 4 Somewhat thick
_____ 5 Very thick
_____ 6 Refuse to answer

14 In general when you have insertive anal intercourse, is the lubricant applied…[Indicate all that apply]

_____ 1 Directly on your penis?
_____ 2 On the outside of your partner's anus (rim)?
_____ 3 Inside your partner's anus?
_____ 4 Inside the condom?
_____ 5 On the outside of the condom?
_____ 6 Other (please specify):_____
_____ 7 Refuse to answer

15 When you are having insertive anal intercourse, who applies the lubricant?

_____ 1 Self
_____ 2 Partner
_____ 3 Both
_____ 4 Refuse to answer

16 When is the lubricant first applied?

_____ 1 Before there is any sexual contact
_____ 2 During sex but before penetration
_____ 3 After penetration if you feel the need for it
_____ 4 Refuse to answer

17 How frequently do you usually reapply the commercial lubricant during insertive anal intercourse?

_____ 1 Never
_____ 2 Once
_____ 3 Twice
_____ 4 3 times or more
_____ 5 Refuse to answer

Lubricant Preferences

18 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

19 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

20 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 (please specify): _____
_____ 7 Refuse to answer

21 Do you prefer a lubricant with …

_____ 1 No flavor

_____ 2 Flavor
_____ 3 It doesn't matter
_____ 4 Refuse to answer

22 Do you prefer a lubricant with …
_____ 1 No color/transparent
_____ 2 Color
_____ 3 It doesn't matter
_____ 4 Refuse to answer

23 Do you prefer a lubricant with …
_____ 1 Unscented/ No scent
_____ 2 Scented
_____ 3 It doesn't matter
_____ 4 Refuse to answer

24 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 lid
_____ 4 Can or jar
_____ 5 Single use, like a plastic pouch containing lubricant
_____ 6 Disposable tube
_____ 7 Other (please specify): _____
_____ 8 Refuse to answer

SECTION D. 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 UI 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. "Meth" (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 vaginal or 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 E. HIV TESTING

THE REFUSE TO ANSWER VALUE FOR VARIABLES THAT ARE NOT NOMINAL IS **999** IN THIS SECTION, UNLESS OTHERWISE NOTED.

Now you will be asked a few questions about your HIV status. Remember that this information is completely confidential.

1. Including the test you received to join this study, 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. Before you joined this study, 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 5; OTHERWISE SKIP TO NEXT SECTION]

   _____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

SECTION F. PRIORITIZATION OF HIV-PREVENTION AND RISK PERCEPTION

Using the pull-down numbers that appear to the left of this list below, indicate the level of importance that different issues have in your mind when you are about to have sex with a guy. Use "1st" for the most important issue, and "8th" for the least important one.

1. When I am about to have sex, the most important issues for me are:

[THE COMPUTER SHOULD PRESENT THIS LIST IN A DIFFERENT RANDOM ORDER TO EACH PARTICIPANT]

[ ] a. having a good time, enjoying sex, and getting sexually satisfied
[ ] b. making sure we use condoms
[ ] c. not getting a sexually transmitted disease (STD) or infection (by this, we mean STDs other than HIV)
[ ] d. not passing a sexually transmitted disease (STD) or HIV to my partner
[ ] e. not getting HIV
[ ] f. that my partner will like me
[ ] g. sexually satisfying my partner
[ ] h. communicating our thoughts and feelings with each other

Refuse to answer

PERCEPTION OF RISK

2. How likely is it that you will get HIV in the near future?

1——2——3——4——5——6——7——8——9——10
Very Unlikely — Very Likely

_____ Refuse to answer

3. Why? _____

4. Considering your usual sexual behavior, how great is your risk of becoming HIV infected in the near future?

1——2——3——4——5——6——7——8——9——10
Very Low — Very High

_____ Refuse to answer

5. Why?_____

6. How likely is it that you will get an STD in the near future?

1—— 2—— 3——4——5—— 6——7——8—— 9——10

Very Unlikely — Very Likely

_____ Refuse to answer

7. Why? _____

SECTION G. LIKELIHOOD OF MICROBICIDE USE (BASELINE)

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.

1. Before joining this study, how much did you know about microbicides?
    1. I had never heard about microbicides
    2. I knew a little about microbicides but not in detail
    3. I was quite well informed about microbicides
    4. 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.

2. If a 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 **intercourse**?

    1. Very unlikely
    2. Unlikely
    3. Likely
    4. Very likely
    5. Refuse to answer

3. If a 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 **intercourse**, on a scale of 1 to 10?

    1——2——3——4——5——6——7——8——9——10
    Very Unlikely — Very Likely

    Refuse to answer

4. How likely would you be to use it every time you have **intercourse** with a **spouse or steady girlfriend/boyfriend**?

    1——2——3——4——5——6——7——8——9——10
    Very Unlikely — Very Likely

    Refuse to answer

5. How likely would you be to use a microbicidal gel every time you have **intercourse** with a **one-night stand**?

    1——2——3——4——5——6——7——8——9——10

Very Unlikely — Very Likely

Refuse to answer

6. How likely would you be to use a microbicidal gel every time you have **intercourse** with other partners who were neither your **spouse or steady boyfriend/girlfriend**s nor **one-night stand**s?

1——2——3——4——5——6——7——8——9——10

Very Unlikely — Very Likely

Refuse to answer

7. How likely would you be to use a microbicidal gel for intercourse if you were using alcohol or drugs?

1——2——3——4——5——6——7——8——9——10

Very Unlikely — Very Likely

Refuse to answer

That completes the questionnaire. Thank you for your participation.

Participant ID | | | | |

Date ___/___/_____
MM DD YYYY

MTN-012/IPM 010

Product Acceptability and Adherence Questionnaire

Presentation Version

2-10-11 version 1.3

Ross Cranston, M.D., Protocol Chair

Alex Carballo-Diéguez, Ph.D., Co-Investigator

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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 "back" arrow.
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

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 H. PRODUCT ACCEPTABILITY

1. Overall, how much did you like the gel?

   1. Disliked very much
   2. Disliked a little
   3. Liked a little
   4. Liked very much
   5. Refuse to answer

2. Overall how much did you like the gel on a scale of 1 to 10?

   1——2——3——4——5——6——7——8——9——10
   Disliked very much — Liked very much

   Refuse to answer

3. What did you like most about the gel? _____

4. What did you like least about the gel? _____

5. How much did you like the appearance of the gel?

   1——2——3——4——5——6——7——8——9——10
   Disliked very much — Liked very much

   Refuse to answer

6. 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

   Refuse to answer

7. 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

   Refuse to answer
   Don't know, I did not taste the gel

8. 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

Refuse to answer
Don't know, I did not smell the gel

9. 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

Refuse to answer

10. How much did you like how the gel felt on your fingers as it came out of the container?

1—2—3—4—5—6—7—8—9—10
Disliked very much — Liked very much

Refuse to answer

11. How much did you like how the gel felt on your penis immediately after applying it?

1—2—3—4—5—6—7—8—9—10
Disliked very much — Liked very much

Refuse to answer

12. How much did you like how the gel felt on your penis 30 minutes after applying it?

1—2—3—4—5—6—7—8—9—10
Disliked very much — Liked very much

Refuse to answer

13. How much did you like how the gel felt after it dried out?

1—2—3—4—5—6—7—8—9—10
Disliked very much — Liked very much

Refuse to answer

SECTION I. APPLICATION PROCESS

Now you will be asked some questions about applying the gel.

1. On average, after you applied the gel, how long did you wait before putting your clothes back on or going to bed?

   _____ (minutes)

   Refuse to answer

2. Was the product completely dry at the time you put your clothes back on or went to bed?

   1. Never
   2. Some of the time
   3. Most of the time
   4. All of the time
   5. Refuse to answer

3. Did you have any problem applying the gel?

   1. No [SKIP TO NEXT SECTION]
   2. Yes. Please describe the problem that you had applying the gel: _____
   3. Refuse to answer [SKIP TO NEXT SECTION]

SECTION J. ADHERENCE AND CHANGES IN PRODUCT USE

Now we would like to ask you some questions about how you used the gel.

1. How many times did you apply the gel on your penis during the days of the trial? ____
   Refuse to answer
   [DO NOT ALLOW RESPONSE GREATER THAN 8]
   [IF RESPONSE IS LESS THAN 7 ASK QUESTION 2. IF RESPONSE IS 7 OR 8 SKIP TO Q 3]

2. What prevented you from applying the gel every day during the trial period? _____

3. Did you ever use less than the specified amount of gel on the times you used the gel?
   1. No [SKIP TO QUESTION 7]
   2. Yes
   3. Refuse to answer

4. How many times did you use less than the specified amount of gel? _____ times
   [DO NOT ALLOW RESPONSE GREATER THAN 8]

5. When you used less than indicated, about how much did you use?
   1. Three quarters of the dose
   2. Half of the dose
   3. One quarter of the dose
   4. Refuse to answer

6. Please indicate the reason why you used less than the specified amount of gel?
   _____

7. During the trial, did you use any other product on your penis besides the gel the staff gave you or hygiene products?
   1. No
   2. Yes. Please indicate what you used _____
   3. Refuse to answer

8. During the trial, how many times did you masturbate? _____
   Refuse to answer
   [IF RESPONSE IS 0 SKIP TO QUESTION 11]

9. During the trial, when was the last time that you masturbated?
   1. Today
   2. Yesterday
   3. Before yesterday
   4. Refuse to answer

10. The last time you masturbated, did you have the study gel on your penis?
    1. No
    2. Yes
    3. Refuse to answer

11. During the trial, how many times did you have any kind of sex with a partner in which your penis was touched?_____
    Refuse to answer
    [IF RESPONSE IS 0 SKIP TO NEXT SECTION]

12. During the trial, when was the last time that you had sex with a partner in which your penis was touched?
    1. Today
    2. Yesterday
    3. Before yesterday
    4. Refuse to answer

13. The last time when you had sex with a partner in which your penis was touched, did you use a condom?
    1. Yes
    2. No
    3. Refuse to answer

14. The last time when you had sex with a partner in which your penis was touched, did you have the study gel on your penis?
    1. Yes
    2. No
    3. Refuse to answer

SECTION K. EXPERIENCES USING THE GEL

Now you will be asked some questions about problems you may have experienced when using the gel.

1. Thinking about your experiences using the gel, did you experience any stickiness?
   1. None [SKIP TO Q 3]
   2. Some
   3. A lot
   4. Refuse to answer

2. How much were you bothered by stickiness?

1	2	3	4	5	6	7	8	9	10
Not at all									Very much

   Refuse to answer

3. Did you experience any soiling or uncomfortable wetness 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

   Refuse to answer

5. Did you experience any burning or irritation 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 burning or irritation?

1	2	3	4	5	6	7	8	9	10
Not at all									Very much

   Refuse to answer

7. Did you experience any itching 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 the itching?

1——2——3——4——5——6——7——8——9——10
Not at all — Very much

Refuse to answer

9. Did you experience any pain or trauma caused by applying this product?
   1. None [SKIP TO Q 11]
   2. Some
   3. A lot
   4. Refuse to answer

10. 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

Refuse to answer

11. Did the gel feel cold to you?
   1. No [SKIP TO Q 13]
   2. Yes
   3. Refuse to answer

12. How would you describe the cold sensation?

1—— 2—— 3—— 4——5——6——7——8——9——10
Very Unpleasant — Very Pleasant

Refuse to answer

13. Did the gel feel warm to you?
   1. No [SKIP TO NEXT SECTION]
   2. Yes
   3. Refuse to answer

14. How would you describe the warm sensation?

1—— 2—— 3—— 4——5——6——7——8——9——10
Very Unpleasant — Very Pleasant

Refuse to answer

SECTION L. LIKELIHOOD OF PRODUCT USE IN THE FUTURE

Now you will be asked about your likelihood of using the gel in the future.

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 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 **intercourse**?

    1. Very unlikely
    2. Unlikely
    3. Likely
    4. Very likely
    5. Refuse to answer

2. If a 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 **intercourse,** on a scale of 1 to 10?

    1——2——3——4——5——6——7——8——9——10
    Very Unlikely — Very Likely

    Refuse to answer

3. How likely would you be to use a microbicidal gel every time you have **intercourse** with a **spouse or steady girlfriend/boyfriend**??

    1——2——3——4——5——6——7——8——9——10
    Very Unlikely — Very Likely

    Refuse to answer

4. How likely would you be to use a microbicidal gel every time you have **intercourse** with a **one-night stand**?

    1——2——3——4——5——6——7——8——9——10
    Very Unlikely — Very Likely

    Refuse to answer

5. How likely would you be to use a microbicidal gel every time you have intercourse with **other sexual partners**, women or men who were neither **spouse or girlfriend/boyfriend**s nor **one-night stands**?

1——2——3——4——5——6——7——8——9——10
Very Unlikely — Very Likely

Refuse to answer

6. How likely would you be to use a microbicidal gel if you don't use condoms?

1——2——3——4——5——6——7——8——9——10
Very Unlikely — Very Likely

Refuse to answer

7. How likely would you be to use a microbicidal gel every time you have intercourse if you were using drugs or alcohol?

1——2——3——4——5——6——7——8——9——10
Very Unlikely — Very Likely

Refuse to answer

8. How would you feel if your **spouse or girlfriend/boyfriend** used a microbicidal gel?

1——2——3——4——5——6——7——8——9——10
Very against it — Very in favor
Refuse to answer

9. How would you feel if a one-night stand used a microbicidal gel?

1——2——3——4——5——6——7——8——9——10
Very against it — Very in favor
Refuse to answer

10. How would you feel if other sexual partners used a microbicidal gel?

1——2——3——4——5——6——7——8——9——10
Very against it — Very in favor
Refuse to answer

11. How much would you be willing to spend on a microbicidal gel?
    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 (please specify):_____
    5. Refuse to answer

SECTION M. RECOMMENDATIONS

Please help us understand how we could make the gel more attractive to people like you.

1. Would you change anything about the gel's appearance?
    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. 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. If you have any other recommendations, please write your recommendations below.

    _____

    _____

    _____

That completes the questionnaire. Thank you for your participation.

Section 13. Study Reporting Plan

Role on MTN-012/IPM 010	Name	E-mail address
Protocol Statistician	Liza Noonan	liza@scharp.org
Project Manager	Corey Miller	corey@scharp.org
Statistical Research Associate	Marla Husnik	marla@scharp.org
Statistical Research Associate	Jason Pan	zpan@scharp.org
Clinical Affairs Safety Associate	Molly Swenson	mollys@scharp.org
Protocol Programmer	Dara Mendyuk	dara@scharp.org
Reporting Programmer	Cathy Kirkwood	ckirkwoo@scharp.org
Laboratory Programmer	Della Wilson	della@scharp.org
CASI Programmer	Lynda McVarish	lmcv@scharp.org
Data Coordinator	Suzanne Cullers	scullers@scharp.org
Document Specialist	Lori Filipcic	lorif@scharp.org

13.1 Purpose of Study Reporting Plan

The purpose of this reporting plan is to describe the reports that the MTN SDMC (SCHARP) plans to generate for MTN-012/IPM 010.

The specific purposes of this plan are:

- To identify the purpose and content of each report;
- To identify those responsible for the preparation and distribution of each report;
- To identify who should review the reports so that corrective action (if necessary) is taken; and
- To ensure the Protocol Team approves the plan prior to study initiation.

This reporting plan was prepared by the MTN-012/IPM 010 SDMC Project Manager in collaboration with other MTN-012/IPM 010 SDMC staff.

13.2 Study Reports

Table 13-1 lists the reports the SDMC will produce and distribute via email. Table13-2 lists the reports the SDMC will produce and make available via the Atlas website: https://atlas.scharp.org.

Following the tables is a description of each report which includes the purpose of the report, who will prepare the report, and specific components of the report.

Table 13-1: MTN-012/IPM 010 SDMC reports distributed via e-mail

Report Title	Distribution Frequency	Email Distribution List
Data Quality Control (QC)	Every two weeks, or as needed	• Site Study Coordinators • Site Data Managers • FHI CORE Clinical Research Manager • SDMC Project Manager
Clinical Data Quality Control (CQC) Queries	Every two weeks, or as needed	• Site Study Coordinators • Site Data Managers • FHI CORE Clinical Research Manager • SDMC Project Manager
Site Specimen Monitoring	Monthly	• Site Study Coordinator • Network Lab Representative • SDMC Project Manager
Summary Specimen Monitoring	Monthly	• Network Lab Representative • SDMC Project Manager

Table 13-2: MTN-012/IPM 010 SDMC reports posted on Atlas

Report Title	Update Frequency	Atlas Viewing Area
Enrollment and Retention	Daily	unsecure
Visit Adherence and Procedure Completion	Every two weeks	unsecure
Site Data Management Quality	Monthly	unsecure
Safety (PSRT)	One week prior to each scheduled PSRT call	secure
Network Lab Assay Results	Monthly, once NL results are received at the SDMC	unsecure
Study Monitoring Committee (SMC)	As determined by the SMC	• MTN-012/IPM 010 SMC members and observers • MTN-012/IPM 010 Protocol Chair • MTN-012/IPM 010 Site Investigators

13.2.1 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.

13.2.2 Clinic Data Quality (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.

13.2.3 Site Specimen Monitoring Report

Purpose: To monitor storage in LDMS of those specimens marked as “stored” on study CRFs

Prepared by: SDMC Laboratory Programmer

Components: Site-specific listing of all discrepancies between the CRF stored specimen data and LDMS data.

13.2.4 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 of all discrepancies for all sites between the CRF stored specimen data and LDMS data.

13.2.5 Enrollment and Retention Report

Purpose: To monitor participant accrual and retention as reflected by data submitted to the SDMC (via DataFax)

Prepared by: SDMC Protocol Programmer

Components: Enrollment, includes the number of men (circumcised and uncircumcised) enrolled each week and cumulatively. Retention includes: total enrolled (broken down by active, inappropriately enrolled, and lost to follow-up); number expected for a given visit; number not expected for a given visit; and total retention by visit calculated as the number of participants who have completed a visit divided by the total number of participants expected for the visit.

13.2.6 Visit Adherence and Completion Report

Purpose: To assess completion of required visit procedures enumerated over all follow-up visits

Prepared by: SDMC Statistical Research Associate

Components: By site and overall:

- distribution of visits, including the number of days between target and actual visit dates and the number of days between sequential follow-up study visits,

- listing of number and percentage of completed key required procedures, which may include specimen collection, safety lab testing, and genital exam completion.

13.2.7 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, percentage of QCs resolved, QC rate per 100 CRF pages, and mean days to fax in CRF pages. Reported cumulatively and for the previous month.

13.2.8 Safety (PSRT) Report

Purpose: To help the Protocol Safety Review Team (PSRT) monitor study participant safety and tolerability as reflected by adverse experiences and product holds reported to the SDMC (via DataFax)

Prepared by: SDMC Reporting Programmer and SDMC Clinical Affairs Safety Associate

Components: Cumulative AE and product hold/discontinuation data reported to SDMC via SCHARP DataFax. Report may include other DataFax data as requested by the PSRT.

13.2.9 Network Lab Assay Results Report

Purpose: To monitor the receipt of lab assay results from the Network Lab

Prepared by: SDMC Laboratory Programmer

Components: For each specimen analyzed by a Network Lab, the number of results expected (per CRF data) along with the number and percentage of results received and processed at SCHARP.

13.2.10 Study Monitoring Committee Report

Purpose: To monitor study progress at each site.

Prepared and distributed by: Prepared by SDMC MTN-012/IPM 010 staff and distributed by SDMC Project Manager

Components: Summary by site and for the study overall of study design and history, accrual, retention, demographics, visit adherence, and safety/adverse events. Site data management quality, and other components as requested by the SMC.