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:

Added:

Marla Husnik, MS
SDMC Statistical Research Associate
SCHARP-FHCRC
1100 Fairview Avenue North, M2-C200
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-5633
Fax: 206-667-4812
Email: marla@scharp.org

Zhenyu (Jason) Pan, MS
SDMC Statistical Research Associate
FHCRC-SCHARP
1100 Fairview Avenue North, M2-C200
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7180
Fax: 206-667-4812
Email: zpan@scharp.org

Added (continued):

Marina Mabragana, MD
BRWG Team
HIV Center for Clinical and Behavioral Studies
1051 Riverside Dr., Unit 15
New York, NY 10032 USA
Phone: 212-543-4237
Fax: 212-543-5385
Email: mabraga@pi.cpmc.columbia.edu

Brid Devlin, PhD
Executive Vice President of Product Development
8401 Colesville Rd., Suite 200
Silver Spring, MD 20910 USA
Phone: 301-608-2221
Fax: 301-608-2241
Email: bdevlin@ipmglobal.org

Updated:

Beth Galaska Burzuk, MID
Protocol ~~Specialist~~Development Manager
Microbicide Trials Network
204 Craft Ave.
Pittsburgh, PA 15213 USA
Phone: 412-641-5579
Fax: 412-641-6170
Email: galaskaburzukb@upmc.edu

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:
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US National Institute of Mental Health
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IPM IND# 69,022

Protocol Chair:
Ross D. Cranston MD, FRCP

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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Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

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

PROTOCOL TEAM ROSTER

Protocol Chair

Ross D. Cranston, MD, FRCP
Protocol Chair
Division of Infectious Diseases
University of Pittsburgh Medical Center
Keystone Building, Suite 510
3520 Fifth Ave.
Pittsburgh, PA 15213 USA
Phone: 412-383-2054
Fax: 412-383-2900
Email: rdc27@pitt.edu

Site Investigators

Ross D. Cranston, MD, FRCP
Site Investigator
Division of Infectious Diseases
University of Pittsburgh Medical Center
Keystone Building, Suite 510
3520 Fifth Ave.
Pittsburgh, PA 15213 USA
Phone: 412-383-2054
Fax: 412-383-2900
Email: rdc27@pitt.edu

Craig Hoesley, MD
Site Investigator
University of Alabama at Birmingham
1530 3rd Ave. South
BDB 467 Box 20
Birmingham, AL 35294 USA
Phone: 205-934-3365
Fax: 205-975-3232
Email: choesley@uab.edu

US National Institutes of Health (NIH)

Roberta Black, PhD
Microbicide Research Branch Chief
Division of AIDS (DAIDS)/National Institute
of Allergy and Infectious Diseases (NIAID)/
National Institutes of Health (NIH)
6700 B Rockledge Dr.
Bethesda, MD 20817 USA
Phone: 301-496-8199
Fax: 301-402-3684
Email: rblack@niaid.nih.gov

Andrew D. Forsyth, PhD
Program Chief
National Institute of Mental Health (NIMH)
6001 Executive Blvd.
Bethesda, MD 20892 USA
Phone: 301-443-8403
Fax: 301-443-9719
Email: aforsyth@mail.nih.gov

Lydia E. Soto-Torres, MD, MPH
DAIDS Medical Officer
Division of AIDS/NIAID/NIH
6700 B Rockledge Dr.
Bethesda, MD 20892-7628 USA
Phone: 301-594-9705
Fax: 301-402-3684
Email: lsoto-torres@niaid.nih.gov

International Partnership for Microbicides

Sepideh Habibi, MD
IPM Medical Safety Physician
8401 Colesville Rd., Suite 200
Silver Spring, MD 20910 USA
Phone : 301-608-2221
Fax : 301-608-2241
Email : shabibi@ipmglobal.org

Annalene Nel, MBChB, PhD
IPM Chief Medical Officer
121 Main St.
Paarl, 7620 South Africa
Phone: +27 21 860 2300
Fax: +27 21 860 2308
Email: anel@ipmglobal.org

Joseph Romano, PhD
IPM Chief Product Development
8401 Colesville Rd., Suite 200
Silver Spring, MD 20910 USA
Phone: 301-608-2221
Fax: 301-608-2241
Email: jromano@ipmglobal.org

Shanique Smythe
IPM Project Manager
IPM Representative
8401 Colesville Rd., Suite 200
Silver Spring, MD 20910 USA
Phone: 301-608-2221
Fax: 301-608-2241
Email: ssmythe@ipmglobal.org

Microbicide Trials Network (MTN) Coordinating and Operations Center (CORE) - Pitt

Katherine Bunge, MD
Protocol Safety Physician
Magee-Womens Hospital of UPMC
300 Halket St.
Pittsburgh, PA 15213 USA
Phone: 412-641-3464
Fax: 412-641-1133
Email: kbunge@mail.magee.edu

Charlene S. Dezzutti, PhD
BSWG Representative
Microbicide Trials Network
204 Craft Ave.
Pittsburgh, PA 15213 USA
Phone: 412-641-3462
Fax: 412-641-6170
Email: dezzuttics@upmc.edu

Beth Galaska Burzuk, MID
Protocol Specialist
Microbicide Trials Network
204 Craft Ave.
Pittsburgh, PA 15213 USA
Phone: 412-641-5579
Fax: 412-641-6170
Email: galaskaburzukb@upmc.edu

Sharon Hillier, PhD
Principal Investigator
Microbicide Trials Network
204 Craft Ave.
Pittsburgh, PA 15213 USA
Phone: 412-641-8933
Fax: 412-641-6170
Email: shillier@mail.magee.edu

Cindy Jacobson, PharmD
Director of Pharmacy Affairs
Microbicide Trials Network
204 Craft Ave.
Pittsburgh, PA 15213 USA
Phone: 412-641-8913
Fax: 412-641-6170
Email: cjacobson@upmc.edu

Ian McGowan, MD, PhD, FRCP
Co-Principal Investigator
Microbicide Trials Network
204 Craft Ave.
Pittsburgh, PA 15213 USA
Phone: 412-641-8999
Fax: 412-641-6170
Email: imcgowan@pitt.edu

Sharon A. Riddler, MD, MPH
Protocol Physician
Univ. of Pitt., Keystone Building, Suite 510
3520 Fifth Ave.
Pittsburgh, PA 15213 USA
Phone: 412-383-1741 or 412-383-1675
Fax: 412-383-2900
Email: riddler@dom.pitt.edu

Devika Singh, MD, MPH
Protocol Safety Physician
Box 359927
Department of Global Health
International Clinical Research Center
325 Ninth Ave.
Seattle, WA 98104 USA
Phone: 206-744-8311
Fax: 206-520-3831
Email: dsingh@u.washington.edu

MTN Network Laboratory (NL)

Charlene S. Dezzutti, PhD
Network Laboratory Director
Microbicide Trials Network
204 Craft Ave.
Pittsburgh, PA 15213 USA
Phone: 412-641-3462
Fax: 412-641-6170
Email: dezzuttics@upmc.edu

Wayne Hall MT(ASCP)
Clinical Laboratory Representative
Microbicide Trials Network
204 Craft Ave. Room A534
Pittsburgh, PA 15213 USA
Phone: 412-641-6956
Fax: 412-641-6170
Email: hallwb@mwri.magee.edu

Lorna Rabe, BS, M(ASCP)
MTN Laboratory Manager
Microbicide Trials Network
204 Craft Ave. Room A530
Pittsburgh, PA 15213 USA
Phone: 412-641-6042
Fax: 412-641-6170
Email: rabelk@upmc.edu

MTN CORE – FHI

Lisa Levy, MPH
Clinical Research Manager
FHI
P.O. Box 13950
Research Triangle Park, NC 27709 USA
Phone: 919-544-7040 Ext. 11260
Fax: 919-544-0207
Email: llevy@fhi.org

Jonathan Paul Lucas, MPH
Community Program Manager
FHI
P.O. Box 13950
Research Triangle Park, NC 27709 USA
Phone: 919-544-7040 Ext. 11458
Fax: 919-544-0207
Email: jlucas@fhi.org

Ashley Mayo, MSPH
Prevention Research Specialist
FHI
P.O. Box 13950
Research Triangle Park, NC 27709 USA
Phone: 919-544-7040 Ext. 11164
Fax: 919-544-7261
Email: amayo@fhi.org

MTN Statistical Data Management Center (SDMC)

Corey Miller, MHS
SDMC Project Manager
Fred Hutchinson Cancer Research Center (FHCRC)-
Statistical Center for HIV/AIDS Research & Prevention (SCHARP)
1100 Fairview Ave. North, LE-400
P.O. Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7672
Fax: 206-667-4812
Email: corey@scharp.org

Liza Noonan, PhD
Protocol Statistician
FHCRC – SCHARP
1100 Fairview Ave. North, M2-C200
P.O. Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7130
Fax: 206-667-4812
Email: liza@fhcrc.org

MTN Behavioral Research Working Group (BRWG)

Alex Carballo-Dieguez, PhD
BRWG Representative
HIV Center for Clinical and Behavioral Studies
1051 Riverside Dr., Unit 15
New York, NY 10032 USA
Phone: 212-543-5261
Fax: 212-543-5385
Email: ac72@columbia.edu

Curtis Dolezal, PhD
BRWG Team
HIV Center for Clinical and Behavioral Studies
1051 Riverside Dr., Unit 15
New York, NY 10032 USA
Phone : 212-543-3597
Fax : 212-543-5385
Email : dolezalc@childpsych.columbia.edu

Rebecca Giguere, MPH
BRWG Team
HIV Center for Clinical and Behavioral Studies
1051 Riverside Dr., Unit 15
New York, NY 10032 USA
Phone: 212-543-5829
Fax: 212-543-5385
Email: giguere@pi.cpmc.columbia.edu

MTN Community Working Group (CWG) Representative

Anne Davis
CWG Representative
University of Pittsburgh CTU
Keystone Building, Suite 510
3520 Fifth Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-3380
Fax: 412-383-1688
Email: davisac@upmc.edu

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

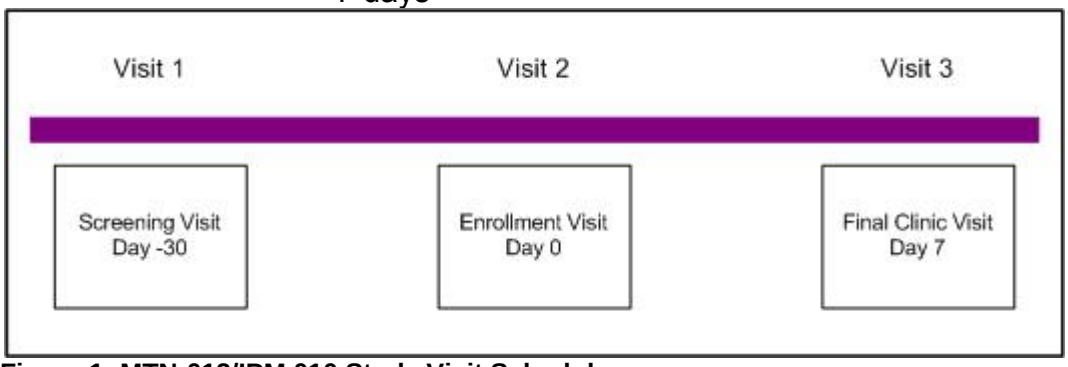


Figure 1: MTN-012/IPM 010 Study Visit Schedule

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.

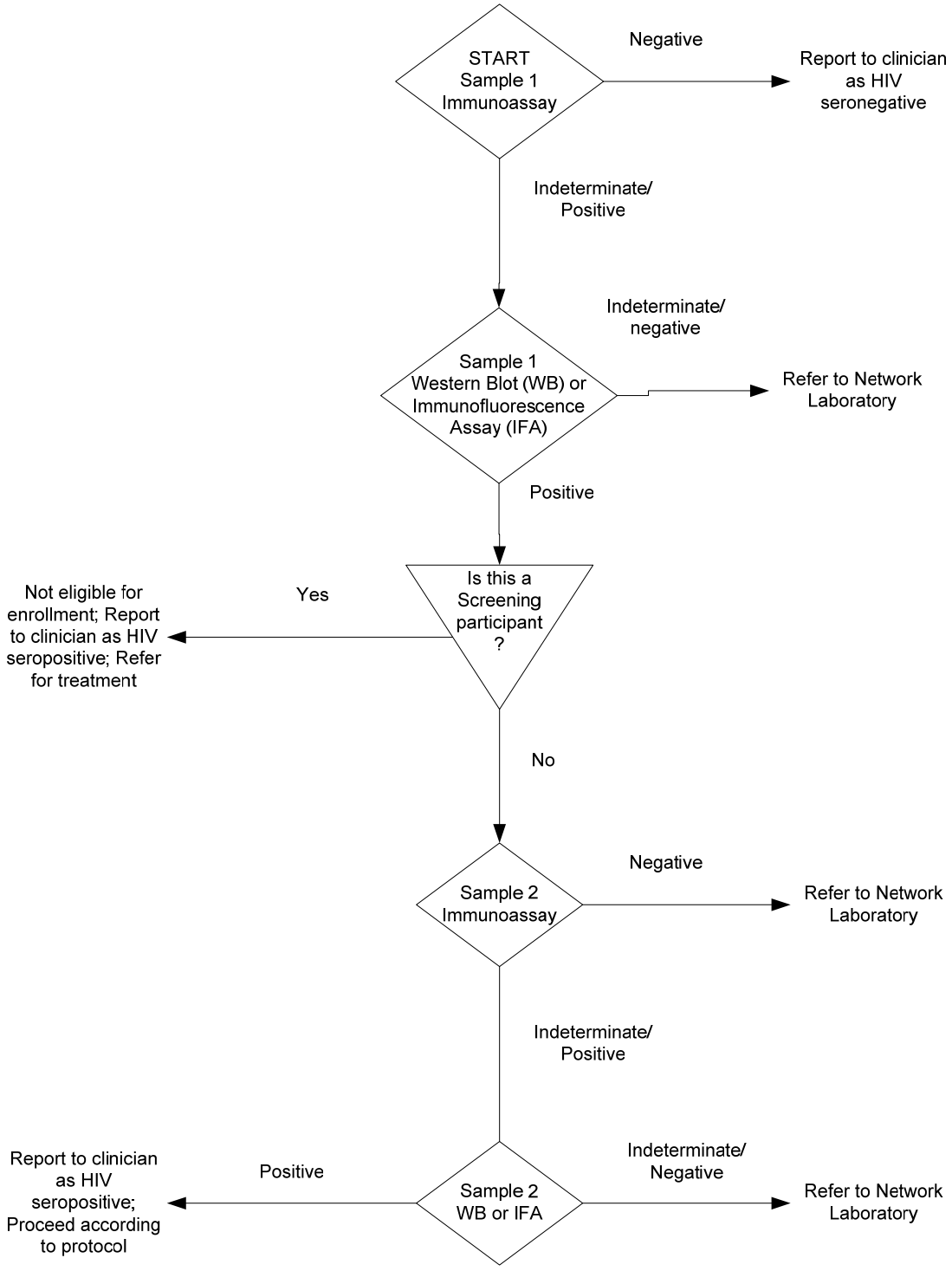
15 APPENDICES

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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