

**MTN-013/IPM 026**

**Phase 1 Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring**

**Microbicide Trials Network**

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**MTN-013/IPM 026**

**Phase 1 Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring**

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## MTN-013/IPM 026

### Phase 1 Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring

#### LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine transaminase
ARV	antiretroviral
ASCCP	American Society for Colposcopy and Cervical Pathology
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
BV	bacterial vaginosis
CAB	community advisory board
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CASI	Computer-Assisted Self Interviewing
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
C <sub>max</sub>	maximum concentration
CORE	Coordinating and Operations Center
CRF	case report form
CRS	Clinical Research Site
CSF	cerebrospinal fluid
CT	<i>Chlamydia trachomatis</i> , chlamydia
CTA	Clinical Trial Agreement
CTU	Clinical Trials Unit
CVF	cervical-vaginal fluid
CWG	Community Working Group
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAPY	di-amino-pyrimidine
DLV	delavirdine
DNA	deoxyribonucleic acid
DSC	differential scanning calorimetry
EAE	expedited adverse event
EC	ethics committees
EFV	efavirenz
EMBRACE	HIV Prevention Agent Pregnancy Exposure Registry
FDA	(US) Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center (FHCRC)
g	grams
GALT	gut-associated lymphoid tissues
GC	<i>Neisseria gonorrhoeae</i> , gonorrhea
GCP	Good Clinical Practices
GEE	Generalized Estimating Equations
GMP	good manufacturing practices
HAART	highly active antiretroviral therapy
hCG	Human Chorionic Gonadotropin

HEC	hydroxyethylcellulose
HEENT	Head, Eye, Ear, Nose and Throat
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HPV	human papillomavirus
hu-PBL	human peripheral blood lymphocytes
hu-SCID	humanized severe combined immunodeficient
IATA	International Air Transport Association
ICF	informed consent form
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	investigational new drug
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
IUD	intrauterine device
kg	kilogram
KLH	Keyhole Limpet Haemocyanin
KOH	potassium hydroxide
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantification
µg	microgram
mg	milligram
mL	milliliter
MO	Medical Officer
MTD	maximum tolerated dose
MTN	Microbicide Trials Network
NAAT	Nucleic Acid Amplification Test
ng	nanogram
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NL	network laboratory
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no-observed-adverse-effect-level
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OBT	optimized background therapy
OHRP	Office for Human Research Protections
PD	pharmacodynamics
PEP	post-exposure prophylaxis
PI	protease inhibitor
PK	pharmacokinetics
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development, Inc.
PRO	Protocol Registration Office
PSRT	Protocol Safety Review Team
PTID	participant identification
QD	once daily
RE	Regulatory Entity
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDMC	Statistical Data Management Center

SMC	Study Monitoring Committee
SOP	standard operating procedure
SSP	study specific procedure(s)
STD	sexually transmitted disease
STI	sexually transmitted infection
SUSAR	Suspected, unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
T <sub>max</sub>	time to maximum concentration
UA	urinalysis
UPLC	ultra performance liquid chromatography
UPMC	University of Pittsburgh Medical Center
USA	United States of America
UTI	urinary tract infection
VR	vaginal ring
WB	Western blot
wt	wild-type
w/w	weight/weight



**MTN-013/IPM 026**

**Phase 1 Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring**

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**MTN-013/IPM 026**

**Phase 1 Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring**

**INVESTIGATOR SIGNATURE FORM**

**Version 1.0**

**April 1, 2011**

**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 Holder:**

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 the Microbicide Trials Network (MTN) and International Partnership for Microbicides (IPM) policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, NIAIDS, NIH, NIMH, and IPM for review prior to submission.

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

\_\_\_\_\_  
Name of Investigator of Record

\_\_\_\_\_  
Signature of Investigator of Record

\_\_\_\_\_  
Date

## MTN-013/IPM 026

### Phase 1 Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring

#### PROTOCOL SUMMARY

<b>Short Title:</b>	Safety and PK of a Dapivirine/Maraviroc VR
<b>Clinical Phase:</b>	Phase 1
<b>IND Sponsor:</b>	International Partnership for Microbicides
<b>Protocol Chair:</b>	Beatrice A. Chen, MD, MPH
<b>Protocol Co-chair:</b>	Lori Panther, MD, MPH
<b>Sample Size:</b>	Approximately 48 women
<b>Study Population:</b>	Healthy, HIV-uninfected, sexually abstinent women between the ages of 18-40
<b>Study Sites:</b>	US site(s) selected by the MTN Executive Committee
<b>Study Design:</b>	Multi-site, double-blinded, four-arm, randomized, placebo-controlled trial
<b>Study Duration:</b>	Approximately 7½ weeks per participant, with approximately 6 months for planned accrual
<b>Study Products:</b>	Dapivirine Vaginal Ring (VR) Maraviroc VR Dapivirine/Maraviroc VR Placebo VR
<b>Study Regimen:</b>	Participants will be randomized to the study VRs in a 1:1:1:1 ratio. Participants will insert one VR to be used for a period of approximately 28 days, followed by approximately 24 days with no study product.

#### Primary Objectives:

- Assess and compare safety of VRs containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc, when used continuously for 28 days by healthy, HIV-uninfected, sexually abstinent women, as compared with the placebo VR
- Examine systemic and local pharmacokinetics of dapivirine and maraviroc in vaginal fluid, plasma and tissue during and after 28 days' continuous use of a matrix vaginal ring containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc

### **Primary Endpoints:**

- The primary safety endpoints are the proportion of women in each of the four vaginal ring regimens (25 mg dapivirine, 100 mg maraviroc, 25 mg dapivirine + 100 mg maraviroc, or placebo) with:
  - Genitourinary events Grade 1 or higher as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009), Addendum 1, (Female Genital Grading Table for Use in Microbicide Studies) judged to be related to study product
  - Adverse events Grade 2 or higher as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009)
- The pharmacokinetic endpoints are:
  - Assessments of systemic and local concentrations of dapivirine and maraviroc in plasma, vaginal fluids and cervical tissue, respectively, during and after 28 days' of continuous use of a vaginal ring containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc.

### **Secondary Objectives:**

- Evaluate the acceptability of the study VR in HIV-uninfected sexually abstinent women over 28 days of use
- Evaluate the adherence to the study VR in HIV-uninfected sexually abstinent women over 28 days of use

### **Secondary Endpoints:**

- Participant report of acceptability including genitourinary and emotional (dis)comfort, awareness/feeling during daily activities, ring insertion/removal issues, and willingness to use in the future
- Participant report of frequency of study VR removal/expulsions (voluntary and involuntary) and duration without VR inserted in vagina

### **Exploratory Objectives:**

- Evaluate the HIV inhibitory activity of mucosal secretions and cervical tissue
- Describe potential changes in the vaginal microenvironment
- Evaluate the study VR for the presence of biofilms
- Evaluate the potential relationship between dapivirine and maraviroc levels and participant self-report of adherence

### **Exploratory Endpoints:**

- Measures of HIV-1 inhibition by mucosal secretions and within cervical tissue
- Abnormal vaginal flora as assessed by Gram stain

- Presence of candidate biomarkers of safety and efficacy in mucosal secretions
- Presence of biofilms on study VR surface
- Dapivirine and maraviroc levels measured in returned VR
- Participant report of duration without VR inserted in vagina

**Figure 1: MTN-013/IPM 026 Study Visits**

(-45 Days)	V0	V1	V2	V3	V4	V5	V6	V7	V8
<b>Screening</b>	<b>Enrollment Day 0</b> <i>Ring Insertion</i>	Day 1	Day 2	Day 3	Day 5	Day 7	Day 14	Day 21	Day 28 <i>Ring Removal</i>
									→
		V9	V10	V11	V12	V13	V14		
		Day 29	Day 30	Day 31	Day 35	Day 42	Day 52		

# 1 KEY ROLES

## 1.1 Protocol Identification

Protocol Title: Phase 1 Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring

Protocol Number: MTN-013/IPM 026

Short Title: Safety and PK of a Dapivirine/Maraviroc VR

Date: April 1, 2011

## 1.2 Funders, Sponsor and Monitor Identification

Funding Agencies: Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID)/National Institute of Mental Health (NIMH)/National Institutes of Health (NIH)  
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## **1.5 Data Center**

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## **1.6 Study Operations**

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## 2 INTRODUCTION

### 2.1 Vaginal Rings and Human Immunodeficiency Virus (HIV) Prevention

Results of CAPRISA 004 represent a groundbreaking step in HIV prevention research.<sup>1</sup> This double-blind, randomized controlled trial compared the use of 1% tenofovir gel versus placebo gel (coitally-dependent regimen) in 889 sexually active women in South Africa. Tenofovir gel reduced HIV acquisition by an estimated 39% overall ( $p=0.017$ ). When the results were examined in subgroups by adherence, the reduction of HIV acquisition in the group with greater than 80% adherence was 54%, whereas the reduction in the group with less than 50% adherence was 28%.

These results underscore the need to identify alternative delivery systems that may optimize adherence to antiretroviral-based chemoprevention. Vaginal rings (VR) with the capacity to release drugs over longer periods of time represent one strategy currently hoped to decrease user lapses in adherence. Additionally, these devices will have the capacity to release more than one drug at a time which may reduce the risk of drug resistance through more potent effectiveness against HIV transmission and/or the avoidance of extended periods of inadvertent, single antiretroviral exposure during HIV infection.

The International Partnership for Microbicides (IPM) has joined with the Microbicide Trials Network (MTN) to evaluate the safety of and adherence to a novel combination antiretroviral-based product, the dapivirine-maraviroc VR, in its first clinical trial. This study will evaluate four separate VRs in support of potential future extended safety and effectiveness studies for this strategy: a dapivirine VR, a maraviroc VR, a combination dapivirine-maraviroc VR, and a placebo VR, described further below.

### 2.2 Rationale

MTN-013/IPM 026 is a Phase 1 trial designed to assess the safety and pharmacokinetics of dapivirine and maraviroc when used in combination in a VR, in comparison with a dapivirine only VR and a maraviroc only VR. The safety of all three rings will be compared with the placebo VR. The dapivirine plus maraviroc vaginal ring is a novel product and it is expected to be the first vaginal microbicide ring with two antiretroviral (ARV)-based active pharmaceutical ingredients to be evaluated in a clinical trial.

The rationale for a combination microbicide vaginal ring is based on results from highly active antiretroviral therapy (HAART)<sup>2</sup> and the use of antiretroviral combinations in the prevention of mother-to-child HIV transmission, which have demonstrated the benefit of ARV combinations in the treatment and prevention of HIV infection.<sup>3</sup> Although the effectiveness of this particular combination in HIV prevention has not been evaluated clinically, both maraviroc and dapivirine are highly potent ARVs. Maraviroc acts early in the HIV life-cycle by blocking access to CCR5, making it an attractive microbicide candidate.<sup>4</sup> However, it is not active against viruses using co-receptors other than



CCR5. Dapivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is active against HIV-1 regardless of the co-receptor tropism of the virus.<sup>4</sup> Therefore, there is a strong scientific rationale for the combination of dapivirine with maraviroc in a microbicide.

To date, candidate vaginal microbicides have been formulated predominantly as gels.<sup>5</sup> Multiple safety and efficacy trials with various microbicides have been completed or are currently underway, most of which evaluate microbicides in a gel formulation delivered via a single-use vaginal applicator. This formulation requires that the gel be delivered coitally or daily for effectiveness which may limit product use and acceptability. For a microbicide to be most effective, it is essential that regimen adherence be maximized. Therefore, it is important that a microbicide product is acceptable to users. It is likely that products that can be applied less frequently will be more acceptable and will achieve a higher level of user adherence. While acceptability data is limited on microbicide VRs, contraceptive VRs are well established and have been shown to be highly acceptable.<sup>6</sup> Sustained drug release devices such as vaginal rings that need only be replaced monthly may have acceptability benefits, and therefore adherence advantages over dosage forms that need to be used more frequently.

## **2.3 Dapivirine VR**

### **2.3.1 Description**

Dapivirine, a NNRTI, is a substituted di-amino-pyrimidine (DAPY) derivative with potent antiviral activity against HIV-1. Dapivirine is chemically described as 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzotrile.<sup>7</sup> The dapivirine matrix VR is a flexible ring containing 25 mg of drug substance dispersed in a platinum-catalyzed-cured silicone matrix. Dapivirine is known to be well-suited for delivery via VR, as evidenced by favorable safety and pharmacokinetic data to date and described below. Further information is available in the dapivirine VR investigator's brochure.<sup>8</sup>

### **2.3.2 Mechanism of Action**

Dapivirine is an NNRTI; NNRTIs bind to the HIV reverse transcriptase (RT) enzyme preventing viral replication and therefore the production of infectious virus.

### **2.3.3 Strength of Study Product**

The dapivirine VR will contain 25 mg of dapivirine. This is the same drug load as was used in dapivirine rings previously tested in four trials involving 65 participants, including a 28 day trial (IPM 024) in HIV-uninfected women using Ring-004. The current formulation is a dapivirine matrix vaginal ring containing 25 mg of drug substance dispersed in a platinum-catalyzed-cured silicone matrix. In addition, platinum-catalyzed matrix vaginal rings containing 25 mg of dapivirine were studied in IPM 013 over an approximately 8-week period with a 4-week follow-up among healthy, sexually active, HIV-uninfected women. The results of these two trials are being finalized.

## **2.4 Maraviroc VR**

### **2.4.1 Description**

Maraviroc is a CCR5 co-receptor antagonist. Maraviroc is chemically described as 4,4-difluoro-N-((1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)cyclohexanecarboxamide. Maraviroc is a white to pale-colored powder with a 513.67 molecular weight. It is highly soluble across the physiological pH range (pH 1.0 to 7.5). In oral form (150 mg and 300 mg tablets) as Selzentry<sup>®</sup>, it is indicated for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1.

The maraviroc matrix VR is a flexible ring containing 100 mg of drug substance dispersed in a platinum-catalyzed-cured silicone matrix. This novel product is designed to release drug over time.

### **2.4.2 Mechanism of Action**

Maraviroc, a CCR5 co-receptor antagonist, selectively binds to the human chemokine receptor CCR5 present on the cell membrane, preventing the interaction of HIV-1 gp120 and CCR5 necessary for CCR5-tropic HIV-1 to enter cells. Since CCR5 is known to be the primary co-receptor involved in sexual transmission of HIV, maraviroc has good potential as a topical microbicide.<sup>4</sup>

### **2.4.3 Strength of Study Product**

The strength of the maraviroc VR will be 100 mg.

## **2.5 Dapivirine/ Maraviroc VR**

### **2.5.1 Description**

The dapivirine/maraviroc matrix VR is a flexible ring containing 25 mg of dapivirine and 100 mg maraviroc dispersed in a platinum-catalyzed-cured silicone matrix. This VR is a novel combination product (drug/device) designed to release both drugs over time.

### **2.5.2 Mechanism of Action**

Please see Sections 2.3.2 and 2.4.2 above.

### **2.5.3 Strength of Study Product**

The strength of the dapivirine/maraviroc VR will be 25 mg of dapivirine and 100 mg of maraviroc.

## 2.6 Placebo VR

### 2.6.1 Description

The placebo VR is a flexible, platinum-catalyzed-cured silicone matrix ring which contains no active drug.

### 2.6.2 Mechanism of Action

The placebo VR is designed to be inactive in the vagina.

### 2.6.3 Strength of Study Product

The placebo VR contains no active drug.

## 2.7 *In vitro* Studies

### 2.7.1 *In vitro* Studies of Dapivirine

#### 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<sub>50</sub>) 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.<sup>9,7</sup>

#### Resistance

HIV-1 virus breakthrough in the presence of dapivirine was initially evaluated in studies in which cells were infected with wild-type HIV-1 laboratory strains at high multiplicity of infection and in the presence of high concentrations of dapivirine. At 40 nM virus breakthrough occurred between 4 and 7 days, at 200 nM between 7 and 10 days and at 1 μM it took up to 30 days to observe virus growth. In all cases mutations were present. Virus selected with the Y181C mutation was resistant to dapivirine. Subsequently, cells were infected with wild-type HIV-1 at low multiplicity of infection and were exposed to very low concentrations of dapivirine in order to mimic the extremely low systemic concentrations observed in the first clinical trial of one formulation of topical dapivirine (Gel-001).

In the first experiment, population sequencing performed following prolonged exposure of HIV-1/LAI-infected MT4 cells to low concentrations of dapivirine for a period of approximately 30 days identified several NNRTI resistance-associated mutations, including Y181C, at dapivirine concentrations of 10 nM and 100 nM, but not at 1 nM and 0.1 nM concentrations. However, both Y181C and V179I were detected when single

viral genomes were analyzed by end-point dilution at 1 and 0.1 nM concentrations. The frequency of Y181C was 10-12% both at 1 and 0.1 nM.

In a second series of experiments using the same and lower dapivirine concentrations, population sequencing identified the Y181C mutation at 1 nM, but not at lower concentrations. Analysis using a more sensitive end-point dilution technique in which the genotypic sequence of 25 to 30 individual viral genomes was determined indicated the presence of Y181C at 0.1 nM, and possibly 0.01 nM (approximately 10-fold lower than the EC<sub>50</sub> for dapivirine).

The significance of Y181C in a single clone at 0.01 nM in the 31-day culture is not clear. It is possible that the sensitive single genome sequencing technology detected some of the pre-existing natural variants present in a virus population in the absence of selective pressure. It was concluded that prolonged exposure to low concentrations of dapivirine can result in selection of viruses carrying NNRTI resistance-associated mutations, but the clinical relevance of these *in vitro* data is not known.<sup>7</sup>

### **Cross-resistance**

In comparison with NVP, delavirdine (DLV), efavirenz (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<sub>50</sub> 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, DLV, 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.<sup>7</sup>

## **2.7.2 *In vitro* Studies of Maraviroc**

### **Anti-HIV Activity**

Maraviroc inhibits the replication of CCR5-tropic laboratory strains and primary isolates of HIV-1 in models of acute peripheral blood leukocyte infection.<sup>10</sup> The mean EC<sub>50</sub> value (50% effective concentration) for maraviroc against HIV-1 group M isolates (subtypes A to J and circulating recombinant form AE) and group O isolates ranged from 0.1 to 4.5 nM (0.05 to 2.3 ng/mL) in cell culture. When used with other antiretroviral agents in cell culture, the combination of maraviroc was not antagonistic with NNRTIs (delavirdine, efavirenz and nevirapine (NVP)), nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine and zidovudine), or protease inhibitors (PI) (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir). Maraviroc was additive/synergistic with the HIV fusion inhibitor enfuvirtide. Maraviroc was not active against CXCR4-tropic and dual-tropic viruses (EC<sub>50</sub> value >10 µM). The antiviral activity of maraviroc against HIV-2 has not been evaluated.

## **Resistance**

HIV-1 variants with reduced susceptibility to maraviroc have been selected in cell culture, following serial passage of two CCR5-tropic viruses (CC1/85 and RU570). The maraviroc-resistant viruses remained CCR5-tropic with no evidence of a change from a CCR5-tropic virus to a CXCR4-using virus. Two amino acid residue substitutions in the V3-loop region of the HIV-1 envelope glycoprotein (gp160), A316T and I323V (HXB2 numbering), were shown to be necessary for the maraviroc-resistant phenotype in the HIV-1 isolate CC1/85. In the RU570 isolate a 3-amino acid residue deletion in the V3 loop, DΔQAI (HXB2 positions 315–317), was associated with maraviroc resistance. The relevance of the specific gp120 mutations observed in maraviroc-resistant isolates selected in cell culture to clinical maraviroc resistance is not known. Maraviroc-resistant viruses were characterized phenotypically by concentration response curves that did not reach 100% inhibition in phenotypic drug assays, rather than increases in EC<sub>50</sub> values.

## **Cross-resistance**

Maraviroc had antiviral activity against HIV-1 clinical isolates resistant to NNRTIs, NRTIs, PIs and the fusion inhibitor enfuvirtide in cell culture (EC<sub>50</sub> values ranged from 0.7 to 8.9 nM (0.36 to 4.57 ng/mL)). Maraviroc-resistant viruses that emerged in cell culture remained susceptible to the enfuvirtide and the protease inhibitor saquinavir.

### **2.7.3 *In vitro* Studies of Dapivirine and Maraviroc in Combination**

#### **Dapivirine-Maraviroc Ring**

Matrix-type silicone elastomer vaginal rings containing 25 mg of dapivirine and various loadings of maraviroc (50 to 400 mg) were manufactured by reaction injection molding at elevated temperature.<sup>11</sup> Release over 28 days *in vitro* was evaluated for each ring formulation using a sink condition model and ultra performance liquid chromatography (UPLC) analysis for quantitation of release of each microbicide. The solubilities of dapivirine and maraviroc were measured both in silicone oil and elastomer.

The release of each microbicide compound from the vaginal rings was characterized by matrix-type  $t_{1/2}$  kinetics, wherein the daily release rate decreased with time. For the 25-mg dapivirine/100-mg maraviroc combination vaginal rings, the Day 1 dapivirine release was 3135  $\mu\text{g}$  ( $\pm 249$   $\mu\text{g}$ ) declining to 116  $\mu\text{g}$  ( $\pm 15$   $\mu\text{g}$ ) on Day 25, while Day 1 maraviroc release was measured at 3232  $\mu\text{g}$  ( $\pm 73$   $\mu\text{g}$ ) declining to 157  $\mu\text{g}$  ( $\pm 6$   $\mu\text{g}$ ) on Day 25. Over 28 days, similar amounts of each microbicide compound were released from the 25/100 mg vaginal rings (11.2 mg maraviroc and 10.3 mg dapivirine) despite a 4-fold difference in initial loadings, suggesting a lower solubility of maraviroc in the silicone elastomer matrix, as confirmed by the results of solubility studies. Differential scanning calorimetry (DSC) analysis demonstrated that each microbicide compound is present predominantly as a crystalline dispersion within the vaginal rings, while scanning Raman microscopy provided a measure of the distribution of each microbicide in the matrix. Based on these results, microbicide combinations may be effectively incorporated within a single matrix-type vaginal ring device to provide sustained release of each microbicide at rates independently determined by their initial loading.

## **Dapivirine-Maraviroc Gel**

### **Activity in TZM-bl Cells**

In an experiment to evaluate the activity of maraviroc in combination with dapivirine in TZM-bl cells, a 70% reduction in the IC<sub>50</sub> of maraviroc was demonstrated.

### **Activity in Tissue Explants**

A combination of maraviroc and dapivirine resulted in a 95% reduction in maraviroc IC<sub>50</sub> and a 52% reduction in the dapivirine IC<sub>50</sub> against HIV-1<sub>BaL</sub> in colorectal tissue explants.

## **2.8 Nonclinical Studies**

Animal study data in multiple species support the safety of dapivirine and maraviroc for further investigation in human trials.

### **2.8.1 Nonclinical Studies of Dapivirine**

#### **Pharmacokinetics**

Systemic exposure to dapivirine was low following vaginal administration of dapivirine gels to rabbits.<sup>7</sup> 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 area under the curve (AUC)<sub>0-24</sub>-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 <sup>14</sup>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.<sup>7</sup>

#### **Toxicology**

The toxicity of dapivirine has been evaluated in a comprehensive program of preclinical studies. These are described in the Investigator's Brochure and included repeat dose vaginal toxicity studies in rabbits using gel formulations of dapivirine at concentrations up to 20 mg/mL for 14 days, up to 5 mg/mL for 13 weeks or up to 2 mg/mL for 39 weeks (dose volume = 1 mL/day). No local or systemic toxicity was identified in any of these

studies. In addition, studies of up to 26 weeks duration were completed in rats and dogs via the oral route. The no-observed-adverse-effect-level (NOAEL) in both species following oral administration was 20 mg/kg/day.  $C_{max}$  at the NOAEL was 0.39 µg/mL in rats and 1.21 µg/mL in dogs, which was more than 1000 and 3400 times, respectively, the maximum mean plasma concentration (0.355 ng/mL) in women using a dapivirine ring (Ring-004) for 28 days. AUC at the NOAEL was 4.80 µg.h/mL in rats and 12.98 µg.h/mL in dogs, which is over 1500 and 4200 times, respectively, the mean AUC (3.022 ng.h/mL) in women using Ring-004 for 28 days.

### **Mutagenesis**

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 Deoxyribonucleic Acid (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).

Vaginal reproductive toxicity trials in rats and rabbits using a formulation of dapivirine gel (Gel-001) at nominal concentrations up to 3.3 mg/mL (10 mM) or another formulation of dapivirine gel (Gel-002) at up to 2.0 mg/mL (0.2%) did not identify any adverse effects on the maternal animals or the developing embryo/fetus.

### **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 hydroxyethylcellulose (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.<sup>7</sup>

## 2.8.2 Nonclinical Studies of Maraviroc

### Pharmacokinetics

Following oral administration maraviroc is absorbed rapidly with a  $T_{max}$  of 4h or less across species. Bioavailability was low in the rat at 5% and absorption was judged to be incomplete based upon hepatic portal vein concentration data. In dogs bioavailability was higher at around 41% and absorption was also judged to be high based upon anticipated first-pass extraction. In humans, due to non-proportionality of pharmacokinetics, absolute bioavailability is dose dependent (23% at 100 mg). In a 4-week intravaginal toxicity study in rabbits using 0.3, 1 and 3% gels (1 mL/day), systemic exposure appeared to be less than proportional to dose and increased with repeated administration. In a 13-week intravaginal study in rabbits in which dapivirine (0.2 and 0.5%) was administered in gels (1 mL/day) in combination with maraviroc (0.1, 1 and 3%), systemic exposure to each drug increased with increasing dose. There was no evidence of any pharmacokinetic drug interactions between dapivirine and maraviroc.

Maraviroc has a volume of distribution in rats, dogs and humans which is significantly above that of total body water ( $>0.7$  L/kg) indicating extensive tissue distribution. Maraviroc, however, shows limited penetration into the brain with a cerebrospinal fluid (CSF) to plasma concentration ratio of 0.01 for unbound drug in the rat. Tissue distribution studies showed that following [ $^3$ H]-labeled maraviroc administration to pigmented rats, there was significant binding of drug-related material to melanin in the eye. Such melanin binding is often observed for lipophilic and basic compounds and is not generally associated with any toxicological consequences. In addition, radioactivity was shown to be associated with lymph nodes (including gut-associated lymphoid tissues (GALT)) following administration of [ $^{14}$ C]-maraviroc to rats. The plasma protein binding of maraviroc is moderate across species with values of 58.0%, 51.0%, 66.0%, 63.7%, 48.4% and 75.5% in mouse, rat, rabbit, dog, cynomolgus monkey and human, respectively. Maraviroc shows some partitioning into red blood cells with partition ratios less than unity in all species except rat.

Unchanged drug was the major excreted component in all species, with combined urine and fecal excretion ranging from 33% of total administered dose in humans to 79% in rats. Metabolism was responsible for the remaining clearance of maraviroc with a high degree of commonality observed across species. The major metabolic pathways involve oxidation of the triazole moiety, N-dealkylation adjacent to the tropane ring, and oxidation in the difluorocyclohexyl ring. The major circulating component was unchanged maraviroc in all species. In addition to unchanged maraviroc (33%), significant metabolites detected in human plasma were a secondary amine product of N-dealkylation (UK-408,027; 22%) and a hydroxylated analogue (11%). All human metabolites were identified in at least one of the toxicology species indicating that animals were exposed to these metabolites in repeat dose safety studies.

Investigations using human liver microsomes and recombinant enzymes have shown that maraviroc is predominantly metabolized by CYP3A4. Consequently its



pharmacokinetics may be altered by co-administered drugs that inhibit or induce this enzyme. Maraviroc itself does not inhibit the activity of any of the major cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4) at clinically relevant concentrations ( $IC_{50} > 30 \mu M$ ).

### **Toxicology**

In acute toxicity studies, the oral NOAEL in mice and rats was 2000 mg/kg. Intravenous doses resulted in death at 200 mg/kg, with a NOAEL of 20 mg/kg.

Repeat-dose studies in CD-1 mice were associated with mortality and slight to mild degenerative changes to the superficial epithelium of the cecum at oral daily doses of 1000 and 2000 mg/kg and no adverse effects at 750 mg/kg. Maraviroc was also well tolerated in rasH2 transgenic mice at daily doses of up to 1500 mg/kg for up to 6 months. In a 1-month oral range-finding study in male rats, 1500 mg/kg induced clinical signs of salivation, diarrhea, decreases in body weight and food consumption, dilatation of colon and cecum and pituitary vacuolation. In addition, two rats had moderate increases in liver enzymes, associated in one rat with liver necrosis. The NOAEL was 300 mg/kg. In a 6-month study in rats, body weight was reduced in males at 900 mg/kg. The liver was confirmed as the principal target organ, with changes in the bile duct (vacuolation from 100 mg/kg and hyperplasia from 300 mg/kg) and hepatocytes (altered cell foci and multinucleated cells at 900 mg/kg). The hepatic changes in males at 300 and 900 mg/kg were still present after a 3-month reversibility period, but thyroid follicular cell hypertrophy at these doses was shown to be reversible. An exploratory study to investigate thyroid function in rats showed that liver enzyme induction contributed to this change. The NOAEL was 100 mg/kg.

In dogs, maraviroc produced a range of clinical signs: emesis from 5 mg/kg, salivation, reddening of the skin and conjunctiva and mydriasis from 10 mg/kg, protruding nictitating membrane, lacrimation from 15 mg/kg and partially closed eyes from 40 mg/kg. The maximum tolerated dose was 150 mg/kg. There were inconsistent reductions in blood pressure in dogs at 50 and 250 mg/kg, and increases in QTc interval from 15 mg/kg. Consequently, the NOAEL was 5 mg/kg in dogs.

Oral administration to monkeys at 800 mg/kg was not well tolerated. Animals were euthanized due to severe clinical signs (prostration, decreased activity, loss of balance, and vomiting) and cardiovascular effects (QT prolongation, decreased heart rate, and lowered diastolic blood pressure). Treatment at 400 mg/kg produced similar, though less severe, findings. After treatment for 9 months, body weight in males was reduced at 120 and 400 mg/kg. Decreases in blood pressure, heart rate and increases in QTc interval occurred at 400 mg/kg. The NOAEL was 120 mg/kg. In a 4-week oral immunotoxicology study in monkeys, daily treatment at up to 300 mg/kg (150 mg/kg twice daily (BID)) did not affect lymphocyte subset distribution, Natural Killer cell activity, macrophage phagocytotic activity or oxidative burst. All animals were able to mount a humoral primary (IgM) and secondary (IgG) immune response against Keyhole Limpet Haemocyanin (KLH), and there were no adverse pathological changes to the immune system.

In a 4-week study in rabbits, intravaginal administration of 0.3, 1 or 3% maraviroc (1 mL/day) did not cause any systemic toxicity. Microscopic findings in the vagina were generally graded as minimal.

### **Mutagenicity**

Maraviroc was not genotoxic in the reverse mutation bacterial test (Ames test in Salmonella and E. coli), a chromosome aberration test in human lymphocytes and rat bone marrow micronucleus test.

### **Reproductive Toxicity**

Maraviroc did not impair mating or fertility of male or female rats and did not affect sperm of treated male rats at up to 1000 mg/kg. Embryofetal development studies in rats (up to 1000 mg/kg) and rabbits (up to 200 mg/kg) revealed an increase in pre-implantation loss in rats at 1000 mg/kg (no effect at 300 mg/kg), but there was no evidence of harm to the fetus in either species. During the pre- and postnatal development studies, the only effect in the offspring was a slight increase in motor activity at 1000 mg/kg in male rats at both weaning and as adults, while no effects were seen in females. Other developmental parameters of the offspring, including fertility and reproductive performance, were not affected by the maternal administration of maraviroc.

### **Carcinogenicity**

Long-term oral carcinogenicity studies of maraviroc were carried out in rasH2 transgenic mice (6 months) and in rats for up to 96 weeks (females) and 104 weeks (males). No drug-related increases in tumor incidence were found in mice at up to 1500 mg/kg/day. In rats, an increase in thyroid adenomas, associated with adaptive liver changes, was observed in male and female rats at 900 mg/kg, but tumor incidence was unaffected at 500 mg/kg.

## **2.8.3 Nonclinical Studies of Dapivirine and Maraviroc in Combination**

### **Toxicology**

In a 13-week study in rabbits in which maraviroc (0.3, 1 or 3%) was administered alone or in combination with dapivirine (0.2 or 0.5%)(1 mL/day) gel, no systemic toxicity was observed, but vaginal irritation was evident in animals that received 3% maraviroc, whether alone or in combination with dapivirine. There was no evidence that the presence of dapivirine exacerbated the toxicity of maraviroc, or vice versa. The NOAELs were considered to be 1% for maraviroc and 0.5% for dapivirine.

### **Biocompatibility**

The following biocompatibility studies will be conducted prior to initiation of MTN-013/IPM 026 using extracts from the dapivirine-maraviroc IR in polar and non-polar solvents:

## **Cytotoxicity**

- Cytotoxicity study using the elution method; extract in minimal essential medium (37°C for 24 hours)

## **Sensitization**

- Guinea pig maximization study; extracts in 0.9% sodium chloride solution (121°C for 1 hour) and sesame oil, NF (121°C for 1 hour)

## **Genotoxicity**

- Bacterial reverse mutation study; extracts in 0.9% sodium chloride solution (121°C for 1 hour) and dimethyl sulfoxide (70°C for 24 hours)
- Mouse lymphoma assay; extracts in serum free cell culture media (37°C for 72 hours) and dimethyl sulfoxide (70°C for 24 hours)

## **Irritation and subacute/subchronic toxicity**

- Rabbits dosed intravaginally, daily, for 35 days extracts in 0.9% sodium chloride solution (121°C for 1 hour) and sesame oil, NF (121°C for 1 hour)

## **2.9 Clinical Studies**

### **2.9.1 Clinical Studies of Dapivirine**

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.<sup>7</sup>

### **Pharmacokinetics**

#### **Dapivirine vaginal rings**

Previously, IPM conducted a 28 day trial (IPM 018) in HIV-uninfected women using tin catalyzed silicone matrix and reservoir rings containing 25 mg of dapivirine. The goal of that trial was to determine the safety and pharmacokinetics (PK) of dapivirine delivered from these rings. The rings were found to be generally safe and well-tolerated with a promising drug release profile.<sup>12</sup>

IPM also conducted a 28-day trial (IPM 024) involving 16 healthy, HIV-uninfected, sexually abstinent women, between the ages of 18 to 40 years of age. The women were randomly assigned (1:1) to a dapivirine (25 mg) matrix ring or a placebo ring for 28 consecutive days. Post-ring insertion (1.5 hr), quantifiable plasma dapivirine concentrations (lower limit of quantification (LLOQ) = 3.00 pg/mL) were observed. These concentrations showed a gradual increase over time, reaching a mean C<sub>max</sub> of 355.0 pg/mL by Day 7 (median T<sub>max</sub>).

The individual plasma dapivirine concentrations did not exceed 1 ng/mL, well below plasma levels at the maximum tolerated dose (MTD) for oral treatment.

For dapivirine in vaginal fluids quantifiable concentrations (LLOQ = 0.40 ng) were also observed by 1.5 h post-ring insertion. Generally, maximum concentrations were reached earlier than in plasma. The highest concentrations were observed in the area near where the ring was placed (mean  $C_{max}$ : 79.9  $\mu\text{g/g}$ ; median  $T_{max}$ : Day 3), followed by the cervix (mean  $C_{max}$ : 66.6  $\mu\text{g/g}$ ; median  $T_{max}$ : Day 4). Dapivirine vaginal fluid concentrations were well above the reported *in vitro*  $IC_{50}$  (50% inhibitory concentration for virus replication) of 0.3 ng/mL in MT4 T cells and the concentration at which greater than 99% inhibition of integrated provirus was observed (3.3 ng/mL) in cervical tissue. On Day 28, prior to ring removal, the mean concentrations ( $C_{pre-ring\ removal}$ ) were 38.6  $\mu\text{g/g}$ , 35.8  $\mu\text{g/g}$  and 13.3  $\mu\text{g/g}$  in the area of the ring, in the cervix and near the introitus, respectively.<sup>4</sup>

By Day 56 (final visit), the plasma dapivirine concentrations of all participants but one were below the LLOQ (3.00 pg/mL) and in all participants vaginal fluid levels were below the LLOQ.

#### Dapivirine Gels 4759 and 4789

The particular formulation of dapivirine planned for this trial is currently being tested in IPM 020 and IPM 014A.<sup>7</sup> IPM 020 is a double-blind, randomized, placebo-controlled Phase 1/2 expanded safety study involving approximately 180 healthy, sexually active, HIV-uninfected 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-uninfected women 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.<sup>7</sup> 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-uninfected, 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 (QD) 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  $AUC_{0-24h}$  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).<sup>4</sup>

## **Safety**

### **Clinical trials of dapivirine vaginal rings**

Across all clinical trials with multiple ring configurations in healthy participants, the dapivirine vaginal ring was generally safe and well tolerated.<sup>4</sup> No serious adverse events (SAEs) were reported in participants using the vaginal ring. One participant, using the placebo ring, experienced two SAEs, bacterial gastroenteritis and pyrexia, which were assessed by the investigator as unrelated to the investigational product. No participants were discontinued from the vaginal ring due to investigational product-related adverse events (AEs). The first dapivirine vaginal ring tested in humans, Ring-001, consisted of two reservoir cores of dapivirine surrounded by a controlled-release outer sheath of silicone elastomer. Ring-001 was tested in a Phase 1, open-label, crossover trial in 12 healthy, sexually abstinent, HIV-uninfected women at a single research centre in Belgium (IPM 001).<sup>13</sup> Women used the placebo ring for 7 days followed by the dapivirine ring for 7 days. There were no SAEs during the trial and few treatment-emergent adverse events (TEAEs). The dapivirine ring was considered to be safe based on the results of this trial in healthy participants.

Ring-002, a similar formulation with a single dapivirine reservoir core, was used in a later clinical trial. Ring-002 was tested in a Phase 1, randomized, placebo-controlled trial conducted at a single research centre in Belgium (IPM 008).<sup>13</sup> The trial included 13 healthy, sexually abstinent, HIV-uninfected women and assessed the feasibility of 7-day use of a silicone elastomer vaginal ring containing dapivirine. Ten women underwent 7-day exposure to dapivirine Ring-002, and three women used a placebo ring for 7 days. There were no SAEs during the trial and few TEAEs. The trial results showed that the dapivirine ring was safe in healthy participants.

Ring-003, a dapivirine matrix vaginal ring containing 25 mg of drug substance dispersed in a tin-catalyzed-cured silicone matrix, was compared with Ring-002 in a Phase 1, randomized, placebo-controlled trial conducted at a single research centre in Belgium. Twenty-four healthy, HIV-uninfected women 18 to 35 years of age were randomly assigned (1:1:1) to dapivirine matrix ring, dapivirine reservoir ring, or placebo ring for 28 consecutive days. No SAEs were reported during the study. No TEAEs were assessed by the investigator as definitely or probably related to the ring, and similar percentages of participants in the dapivirine and placebo ring groups had TEAEs considered to be possibly related to the ring.

The current formulation, Ring-004, is a dapivirine matrix vaginal ring containing 25 mg of drug substance dispersed in a platinum-catalyzed-cured silicone matrix. Ring 004

was tested in a 28 day trial (IPM 024) involving 16 healthy, HIV-uninfected, sexually abstinent women, between 18 to 40 years of age. The women were randomly assigned to a dapivirine (25 mg) matrix ring or a placebo ring for 28 consecutive days. No SAEs were reported in the dapivirine vaginal ring group. No adverse events assessed by the investigator were judged to be related to the study agent. Most dapivirine vaginal ring group participants, 87.5% (7/8), experienced at least one TEAE. Of the women in the dapivirine vaginal ring group who experienced a TEAE, 50% (4/8) reported headache. Two to four women (25% to 50%) with dapivirine vaginal rings experienced Grade 1 or Grade 2 metrorrhagia, vulvovaginal discomfort and nasopharyngitis TEAEs. One participant experienced a Grade 1 vaginal hemorrhage in the dapivirine vaginal ring group.<sup>4</sup>

### **Clinical trials of dapivirine vaginal gel**

#### **Dapivirine Gel 001**

Dapivirine gel was tested in a 2-part, Phase 1 trial (TMC120-C127) in 48 HIV-uninfected women and 16 HIV-positive women.<sup>7</sup> 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.<sup>14</sup>

#### **Dapivirine Gel 002**

To improve solubility and stability, a new vehicle was developed for vaginal delivery of dapivirine.<sup>7</sup> 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.<sup>15</sup> 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 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 QD for 11 days.<sup>7</sup> There were no SAEs or discontinuations due to TEAEs in the trial. Most participants (83-100%) in each group had at least one TEAE during the trial. Headache was the event that occurred most often; 42-67% of participants in the dapivirine gel groups and 42% of participants in the placebo gel group reported at least one headache. For most participants 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 other TEAEs deemed related to the gel included malaise (1/12) and cervix erythema (1/12).

### **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.

### **Pregnancy Outcomes**

There are no adequate and well-controlled studies of dapivirine in pregnant women.

## **2.9.2 Clinical Studies of Maraviroc**

### **Pharmacokinetics**

Peak maraviroc plasma concentrations are attained 0.5–4h following single oral doses of 1–1200 mg administered to uninfected volunteers. The pharmacokinetics of oral maraviroc is not dose-proportional over the dose range.

The absolute bioavailability of a 100 mg dose is 23% and is predicted to be 33% at 300 mg. Maraviroc is a substrate for the efflux transporter P-glycoprotein.

Co-administration of a 300 mg tablet with a high fat breakfast reduced maraviroc  $C_{max}$  and AUC by 33% in healthy volunteers. There were no food restrictions in the studies that demonstrated the efficacy and safety of oral maraviroc.

Maraviroc is bound (approximately 76%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. The volume of distribution of maraviroc is approximately 194L.

Studies in humans and *in vitro* studies using human liver microsomes and expressed enzymes have demonstrated that maraviroc is principally metabolized by the cytochrome P450 system to metabolites that are essentially inactive against HIV-1. *In vitro* studies indicate that CYP3A4 is the major enzyme responsible for maraviroc metabolism. *In vitro* studies also indicate that polymorphic enzymes CYP2C9, CYP2D6 and CYP2C19 do not contribute significantly to the metabolism of maraviroc.

Maraviroc is the major circulating component (~42% drug-related radioactivity) following a single oral dose of 300 mg [<sup>14</sup>C]-maraviroc. The most significant circulating metabolite in humans is a secondary amine (~22% radioactivity) formed by N-dealkylation. This polar metabolite has no significant pharmacological activity. Other metabolites are products of mono-oxidation and are only minor components of plasma drug-related radioactivity.

The terminal half-life of maraviroc following oral dosing to steady state in healthy participants was 14–18 hours. A mass balance/excretion study was conducted using a single 300 mg dose of <sup>14</sup>C-labeled maraviroc. Approximately 20% of the radiolabel was recovered in the urine and 76% was recovered in the feces over 168 hours. Maraviroc was the major component present in urine (mean of 8% dose) and feces (mean of 25% dose). The remainder was excreted as metabolites.

### **Safety**

The safety profile of oral maraviroc is primarily based on 840 HIV-infected participants who received at least one dose of oral maraviroc during two Phase 3 trials.<sup>10</sup> A total of 426 of these participants received the indicated BID dosing regimen. Assessment of treatment-emergent adverse events is based on the pooled data from two studies in participants with CCR5-tropic HIV-1 (A4001027 and A4001028). The median duration of maraviroc therapy for participants in these studies was 48 weeks, with the total exposure on oral maraviroc BID at 309 patient-years versus 111 patient-years on placebo + optimized background therapy (OBT). The population was 89% male and 84% white, with mean age of 46 years (range 17–75 years). Subjects received dose equivalents of 300 mg maraviroc QD or BID.

The most common adverse events reported with oral maraviroc BID therapy with frequency rates higher than placebo, regardless of causality, were upper respiratory tract infections, cough, pyrexia, rash, and dizziness. Additional adverse events that occurred with QD dosing at a higher rate than both placebo and BID dosing were diarrhea, edema, influenza, esophageal candidiasis, sleep disorders, rhinitis, parasomnias, and urinary abnormalities. In these two studies, the rate of discontinuation due to adverse events was 5% for participants who received maraviroc BID plus OBT as well as those who received placebo plus OBT. Most of the adverse events reported were judged to be mild to moderate in severity. The data described below occurred with oral maraviroc BID dosing.

The total number of participants reporting infections were 233 (55%) and 84 (40%) in the oral maraviroc BID and placebo groups, respectively. Correcting for the longer



duration of exposure on maraviroc compared to placebo, the exposure-adjusted frequency (rate per 100 subject-years) of these events was 133 for both maraviroc BID and placebo. Dizziness or postural dizziness occurred in 8% of participants on either maraviroc or placebo, with 2 participants (0.5%) on maraviroc permanently discontinuing therapy (1 due to syncope, 1 due to orthostatic hypotension) versus 1 subject on placebo (0.5%) permanently discontinuing therapy due to dizziness.

### **Pregnancy Outcomes**

There are no adequate and well-controlled studies of maraviroc in pregnant women.

### **Resistance**

Virologic failure on maraviroc can result from genotypic and phenotypic resistance to maraviroc, through outgrowth of undetected CXCR4-using virus present before maraviroc treatment, through resistance to background therapy drugs, or due to low exposure to maraviroc.

Both routes to resistance (outgrowth of CXCR4-using virus or reduced maximal inhibition of CCR5-tropic virus) have been observed in clinical studies of both treatment naïve and treatment experienced patients. CXCR4-using virus presence at virologic failure appears to originate from a pre-existing viral population. Pre-therapy testing for the presence of this viral form can reduce the incidence of failure through this mechanism.

### **2.9.3 Clinical Studies of Placebo VR**

Similar placebo VRs have been studied in two IPM clinical trials; IPM 024 and IPM 013 (see Sections 2.3.3, 2.9.1 and 2.10.4).

## **2.10 Study Hypothesis and Rationale for Study Design**

### **2.10.1 Study Hypothesis**

MTN-013/IPM 026 hypothesizes that all four study VRs will be safe and well-tolerated among healthy, sexually abstinent women. The null hypothesis is that there will be no difference in the safety profile between the active products and the placebo.

### **2.10.2 Rationale for Study Design**

#### **Safety**

Careful assessments of safety, including systemic safety, will be undertaken in MTN-013/IPM 026, with special consideration for issues related to systemic toxicity. The study products evaluated in this trial have potential adverse effects, and tolerance may vary depending on formulation. The design of MTN-013/IPM 026 will allow safety comparisons of each product to a placebo, and may provide some data suggesting relative safety among active products. Most importantly researchers will undertake these questions while protecting the safety of study participants.

## **Rationale for Pharmacokinetics Sampling**

### **Ring In Phase**

Absorption is a function of release from ring and absorption across tissue into blood. With reported rate of release of dapivirine and maraviroc in this formulation, the rise in cervicovaginal fluid (CVF) concentration will likely rise quickly on the day it is inserted. Given the sustained drug release characteristics, it is expected to maintain near steady-state concentrations for the duration of this planned 28 days of ring use. To capture systemic absorption of either drug, blood will be sampled multiple times in the hours and days following ring insertion and then at weekly intervals. To capture the concentrations of either drug within the vagina, CVF will be sampled on nearly a daily basis in the first week and weekly thereafter. A tear strip will be used to adsorb CVF to avoid destructive vaginal sampling with either lavage or direct aspiration, which would remove too much fluid and, therefore, alter resulting CVF concentrations.

Tissue sampling would be highly informative given that it is the likely site of drug action. However, biopsies must be taken sparingly for several reasons: they are painful to some women, they may alter CVF drug concentration, and the presence of a ring *in situ* may alter the healing process. Accordingly, biopsies will be delayed until the ring is removed.

Cytobrush is primarily for capturing cells in the cervical canal. While dapivirine must enter cells for its NNRTI mechanism of action, there is no complex phosphorylation that would create significant differences in intracellular and extracellular kinetics. If there is evidence that dapivirine has different intra- and extracellular kinetics, then cytobrush (and extraction of intact cells from tissue) may be useful. Maraviroc acts at the surface of the cell at the CCR5 receptor, therefore, intracellular concentrations are not believed to be relevant, thus cytobrush collection will not be performed.

### **Ring Out Phase**

After removal of the ring, concentration in tissue, blood, and CVF is a function of release of drug from the vaginal tissue reservoir into the vagina and turnover of CVF due to natural processes. To capture the rate of dapivirine and maraviroc concentration from these compartments; blood, cervical tissue, and CVF (via tear test strips) will be collected at intervals following ring removal. Maraviroc has relatively short blood plasma half-life and is reported to rapidly enter CVF after oral dosing. From this, it is anticipated that maraviroc will release rapidly. Dapivirine, by contrast, will release slowly over time given its greater tissue avidity. Accordingly, frequent blood collections following Day 28 ring removal may be highly informative, especially for maraviroc. The total duration of blood collection is planned to demonstrate that all drug has been eliminated sufficiently to drop below assay detection limits.

CVF drug concentration will be assessed with tear test strips as during the ring in phase with similar sampling scheme in order to track the rate of drug elimination. Biopsies will also be collected after the ring is removed. Paired biopsies will provide the best data as

it will avoid inter-individual variability. Pairing a Day 28 biopsy for all biopsy cohort participants with one other sample time – Day 31, 35, 42 – will provide 2 samples with which to estimate drug half-life in tear test strips following ring removal.

### **2.10.3 Rationale for Naked Eye Safety Assessment**

Colposcopic evaluation of the cervicovaginal epithelium has been used to assess the safety of new microbicide products since the high magnification of a colposcope allows clinicians to recognize epithelial changes such as breaks in the epithelium or inflammation. These epithelial changes may potentially increase the risk of STIs or, alternatively, be of no clinical significance. However, the role of colposcopy in assessing the safety of topically applied microbicides has recently been questioned since colposcopy has not been demonstrated to add to the identification of clinically significant cervicovaginal lesions in comparison to naked eye evaluation.<sup>16</sup>

#### Colposcopic examinations vs. naked eye examinations in the presence of N-9 and placebo gel

In a recent assessment of nine Phase 1 microbicide gel safety studies for which colposcopy data were available, Case Report Forms (CRFs) asking the following question, “Was this colposcopic finding seen on naked eye exam?,” were reviewed.<sup>17</sup>

When all product-related findings across the 9 studies were considered (“product-related” being defined as not present at baseline and not iatrogenic), there were a total of 403 findings, 173 (43%) of which would have been missed if colposcopic examination had not been used. As would be expected, most of these (115 of 173, or 66%) were small findings (< 5mm).

Another question on the CRF further probed how informative would these small findings have been in a comparison of a known “bad actor” (N-9) and placebo gel. In looking only at the study that compared N-9 and placebo gel, the following was found:<sup>18</sup>

**Table 1: Colposcopy vs. Naked Eye Examination Findings**

	A	B	C	D	E
	# of findings seen by naked eye	# of findings seen by colposcopy only	Ratio N-9: Placebo, Findings seen by naked eye (Column A)	Ratio N-9:Placebo, Findings seen by colposcopy only (Column B)	Ratio N-9:Placebo, Findings as seen by both naked eye and colposcopy (Column A & B)
All product-related findings					
N-9	63	13	63:9 = 7.0	13:9 = 1.4	76:18 = 4.2
HEC	9	9			
Small findings (< 5 mm)					
N-9	5	10	5:4 = 1.3	10:7 = 1.4	15:11 = 1.44
HEC	4	7			
Deep disruptions					
N-9	4	0	4:1 = 4.0	0:0	4:1 = 4.0
HEC	1	0			

According to the data in the above table, with regard to all product-related findings, naked eye exam alone suggests that there are 7 times as many findings in the N-9 group than in the HEC group (see column C). When the colposcopic data is evaluated alone this ratio falls to 1.4; making the two products appear quite similar (see column D). Data on small findings and deep disruptions have also been included and offer no evidence that colposcopy is helpful in distinguishing between these two products. For colposcopy to be useful in identifying an unsafe product, it must prove to be more informative and provide more valuable data than naked eye exam alone. In this study, naked eye exam was far more likely than colposcopy to identify N-9 as a dangerous product.

#### Interobserver reliability with regard to colposcopic exams

Numerous studies highlight the problematic nature of interobserver agreement with regard to colposcopic examinations. For example, colposcopy interobserver agreement in the scoring of colposcopic images (digitized and photographs) has been found to be fair to poorly reproducible when used to assess colposcopic findings, specifically; borderline cytology results;<sup>19</sup> cervical dysplasia (unanimous agreement in only 20% of the cases);<sup>20</sup> identification of the area, border and color characteristics of an atypical transformation zone;<sup>21</sup> colposcopic impression; Reid colposcopic index scores; lesion size;<sup>22</sup> number of visible lesions; human papillomavirus (HPV) infection states; and final histological diagnosis.<sup>23</sup> The variability in observer ratings highlights the subjectivity of colposcopy examinations. While reproducible observer findings are not mandatory for MTN-013/IPM 026, documenting genital findings as accurately as possible is critical for providing the most accurate safety analysis possible.

The data presented above suggest that colposcopy does not have a place in larger studies and should therefore be replaced as soon as possible in all larger studies with something that is more objective, reproducible, and validated against an HIV acquisition endpoint. Naked eye examination should be considered a more sensitive methodology for the detection of local findings associated with risk for HIV acquisition. Colposcopy has the potential to dilute safety signals with insignificant findings, potentially making a dangerous product, such as N-9, appear safe.

Given the sensitivity of naked eye exam, the problematic nature of inter-observer agreement with regard to colposcopic examinations, and recent communication from the US Food and Drug Administration (FDA) that colposcopy should be performed in at least one Phase 1 trial conducted in sexually active women, of which this study population is not, MTN-013/IPM 026 will complete comprehensive naked eye examinations to evaluate local safety of maraviroc, dapivirine, maraviroc-dapivirine VRs.<sup>24</sup> This approach will provide data from hundreds of detailed visual eye exams.

#### **2.10.4 Justification of Dosing**

The safety of dapivirine and maraviroc has been demonstrated through the development programs for the individual drug substances. Dapivirine has been investigated during an extensive nonclinical development program evaluating the safety of oral and vaginal microbicide formulations.<sup>4</sup> The oral studies provide valuable information regarding the systemic safety of dapivirine, with systemic exposures at the NOAELs far higher than those in women using dapivirine vaginal gels and rings. Furthermore, no toxicity has been seen in any nonclinical studies in which dapivirine was administered intravaginally, and dapivirine gels and rings have been shown to be safe and well-tolerated in all clinical trials conducted to-date. Maraviroc has been marketed as Selzentry™/Celsentri® for treatment of HIV/AIDS since 2007; the nonclinical development program in conjunction with the established clinical safety profile provides excellent reassurance of the systemic safety of maraviroc when used as a microbicide.

Nonclinical investigations with maraviroc alone and in combination with dapivirine support the safety of the dapivirine and maraviroc combination when used as a vaginal microbicide.<sup>4</sup> The 4-week study in rabbits, in which gels containing maraviroc at concentrations of 0.3%, 1% or 3% were administered intravaginally (1 mL/day), did not cause any systemic toxicity and microscopic findings in the vagina were generally graded as minimal. The drug concentrations in formulations used in the 13-week combination study in rabbits, at which there were considered to be no adverse effects, were 0.5% for dapivirine and 1.0% for maraviroc. Since the dose volume used was 1 mL/day, these translate to daily doses of 5 and 10 mg/rabbit, respectively. The combination ring contains 25 mg of dapivirine and 100 mg maraviroc and is intended for use over a period of 1 month. Therefore, the cumulative exposure of rabbits over a 28-day period was 140 mg for dapivirine and 280 mg for maraviroc, which is 5.6 and 2.8 times higher, respectively, than the maximum theoretical exposure that could occur in women using the ring over the same period. In addition, in a previous clinical trial (IPM

024) in which a ring composed of exactly the same silicone as the combination ring and containing 25 mg of dapivirine was used, the maximum concentration of dapivirine measured in cervicovaginal fluid was 79.9 µg/g. Assuming 1 g = 1 mL, this translates to a concentration more than 60 times lower than the concentration administered at the no effect level in rabbits. It is therefore anticipated that the amount of maraviroc released from the combination ring will also result in local concentrations much lower than that administered to rabbits at the no effect level. Furthermore, the maximum approved dosage for Selzentry®/Celsentri® for treatment of HIV/AIDS in the absence of co-administered CYP3A inhibitors or inducers is 300 mg maraviroc b.i.d. (600 mg/day). This daily dose is therefore 6 times higher than the total maraviroc loading in the combination ring intended for use for 1 month.

In conclusion, the extensive clinical and nonclinical safety data for dapivirine and maraviroc support the clinical use of a vaginal ring containing the combination of these compounds as a microbicide in a carefully monitored Phase I clinical trial.<sup>4</sup>

### **3 OBJECTIVES**

#### **3.1 Primary Objectives**

- Assess and compare safety of VRs containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc, when used continuously for 28 days by healthy, HIV-uninfected, sexually abstinent women, as compared with the placebo VR
- Examine systemic and local pharmacokinetics of dapivirine and maraviroc in vaginal fluid, plasma and tissue during and after 28 days' continuous use of a matrix vaginal ring containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc

#### **3.2 Secondary Objectives**

- Evaluate the acceptability of the study VR in HIV-uninfected sexually abstinent women over 28 days of use
- Evaluate the adherence to the study VR in HIV-uninfected sexually abstinent women over 28 days of use

#### **3.3 Exploratory Objectives**

- Evaluate the HIV inhibitory activity of mucosal secretions and cervical tissue
- Describe potential changes in the vaginal microenvironment

- Evaluate the study VR for the presence of biofilms
- Evaluate the potential relationship between dapivirine and maraviroc levels and participant self-reports of adherence

## **4 STUDY DESIGN**

### **4.1 Identification of Study Design**

MTN-013/IPM 026 is a multi-site, double-blinded, four-arm, randomized placebo-controlled trial.

### **4.2 Summary of Major Endpoints**

- The primary safety endpoints are the proportion of women in each of the four vaginal ring regimens (25 mg dapivirine, 100 mg maraviroc, 25 mg dapivirine + 100 mg maraviroc, or placebo) with:
  - Genitourinary events Grade 1 or higher as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009), Addendum 1, (Female Genital Grading Table for Use in Microbicide Studies) judged to be related to study product
  - Adverse events Grade 2 or higher as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009)
- The pharmacokinetic endpoints will be as follows:
  - Assessments of systemic and local concentrations of dapivirine and maraviroc in plasma, vaginal fluids and cervical tissue, respectively, during and after 28 days' of continuous use of a vaginal ring containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc.

### **4.3 Description of Study Population**

The study population will include 48 healthy 18-40 year old women who are HIV-uninfected, non-pregnant, sexually abstinent and using adequate contraception, as described in Sections 5.2 and 5.3.

### **4.4 Time to Complete Accrual**

The approximate time to complete study enrollment is expected to be 6 months.

## **4.5 Study Groups**

Four study groups are planned. All study groups will be assigned to complete a total of 16 total visits.

The four study groups are as follows:

- 1) Dapivirine VR group
- 2) Maraviroc VR group
- 3) Dapivirine/maraviroc VR group
- 4) Placebo VR group

## **4.6 Expected Duration of Participation**

The expected duration for participants is approximately 7½ weeks, not including the 45 day screening period. No study data will be collected after the 52 Day Final Clinic/Early Termination Visit unless the participant is pregnant at the 52 Day Final Clinic/Early Termination Visit. Participants who have AEs at the 52 Day Final Clinic/Early Termination Visit that have not resolved or stabilized will be followed beyond the 52 Day Final Clinic/Early Termination Visit until a clinically acceptable resolution of the AE(s) is confirmed and documented. Clinical acceptability of resolution will be determined by the site Investigator of Record (IoR) in consultation with the Protocol Safety Review Team (PSRT). Participants who are pregnant at the 52 Day Final Clinic/Early Termination Visit may be followed as per Section 9.6, Pregnancy. .

## **4.7 Sites**

Sites selected by the MTN Executive Committee will participate in MTN-013/IPM 026.

# **5 STUDY POPULATION**

## **5.1 Selection of the Study Population**

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

### **5.1.1 Recruitment**

Participants will be recruited from a variety of sources across sites, including family planning clinics, colleges and universities, and gynecology clinics, as well as community-based locations. Participants also will be referred to the study from other local research projects and other health and social service providers serving the target study population. Recruitment materials will be approved by site Institutional Review



Boards/Ethics Committees (IRBs/ECs) prior to use. Site community representatives should advise on these materials before they are submitted to the IRB/EC for review.

### **5.1.2 Retention**

Once a participant is enrolled/randomized in MTN-013/IPM 026, the study site will make every effort to retain the participants in follow-up to minimize possible bias associated with loss-to-follow-up. Each study site will establish and follow standard operating procedures (SOPs) for participant retention. An average retention rate of 95% will be targeted across sites.

### **5.2 Inclusion Criteria**

Women must meet all of the following criteria to be eligible for inclusion in the study.

- 1) Age 18 through 40 years (inclusive) at screening, verified per site SOPs
- 2) Able and willing to provide written informed consent to be screened for and take part in the study
- 3) Able and willing to provide adequate locator information, as defined by the site SOPs
- 4) HIV-uninfected, based on testing performed by study staff at Screening and Enrollment (per applicable algorithm in Appendix II)
- 5) In general good health at Screening and Enrollment, as determined by the site IoR or designee
- 6) At Screening, participant states willingness to abstain from receptive sexual activity (including oral, vaginal and anal intercourse) for the 14 days prior to enrollment and for the duration of study participation
- 7) Per participant report, using an effective method of contraception at Enrollment, and intending to continue use of an effective method for the duration of study participation. Effective methods include hormonal methods (except contraceptive vaginal rings), intrauterine device (IUD) inserted at least 28 days prior to enrollment, being a woman who identifies as a woman who has sex with women exclusively, sterilization, and/or sexually abstinent for the past 90 days
- 8) Satisfactory Pap result in the 12 calendar months prior to Enrollment consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), or satisfactory evaluation with no treatment required of Grade 1

or higher Pap result per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines in the 12 calendar months prior to Enrollment.

- 9) Per participant report at Screening and Enrollment, agrees not to participate in other research studies involving drugs, medical devices, or vaginal products for the duration of study participation
- 10) Per participant report at Screening, regular menstrual cycles with at least 21 days between menses (does not apply to participants who report using a progestin-only method of contraception at screening, e.g., Depo-Provera or levonorgestrel-releasing IUD)
- 11) At Screening and Enrollment, participant states a willingness to refrain from inserting any non-study vaginal products or objects into the vagina, including but not limited to, spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), douches, lubricants, sex toys (vibrators, dildos, etc.), and tampons for the 5 days prior to enrollment throughout the duration of study participation.

*Note: At the Screening visit participant also agrees to refrain from the practices listed above for at least 5 days prior to enrollment.*

### **5.3 Exclusion Criteria**

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

- 1) Participant report of any of the following at Screening:
  - a. Known adverse reaction to silicone, titanium dioxide, or to any of the components of the study products
  - b. Use and/or anticipated use during the period of study participation of CYP3A inducer(s) and/or inhibitor(s)
  - c. Chronic and/or recurrent candidiasis
  - d. Non-therapeutic injection drug use in the 12 months prior to screening
  - e. Post-exposure prophylaxis for HIV exposure within 6 months prior to screening
  - f. Last pregnancy outcome 90 days or less prior to screening
  - g. Currently breastfeeding
  - h. Hysterectomy
  - i. Intends to become pregnant within the next 4 months
  - j. Has plans to relocate away from the study site area in the next 4 months
- 2) Reports participating in any other research study involving drugs, medical devices, or vaginal products 60 days or less prior to enrollment
- 3) At Screening or Enrollment, as determined by the IoR/designee, any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic,

neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, or at increased risk of cardiovascular events

- 4) Has any of the following laboratory abnormalities at Screening:
- Aspartate aminotransferase (AST) or alanine transaminase (ALT) Grade 1 or higher as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009)
  - Calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula, where creatinine clearance (female) in mL/min =  $(140 - \text{age in years}) \times (\text{weight in kg}) \times (0.85) / 72 \times (\text{creatinine in mg/dL})$
  - Hemoglobin Grade 1 or higher as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009)
  - Platelet count Grade 1 or higher as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009)

*Note: Otherwise eligible participants with an exclusionary test result may be re-tested during the screening process. If a participant is re-tested and a non-exclusionary result is documented within 45 days of providing informed consent for screening, the participant may be enrolled.*

- 5) At Screening or Enrollment, is pregnant
- 6) Diagnosed with urinary tract infection (UTI) at Screening or Enrollment

*Note: Otherwise eligible participants diagnosed with UTI during screening will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 45 days of obtaining informed consent for screening, the participant may be enrolled.*

- 7) Diagnosed with pelvic inflammatory disease, a sexually transmitted infection (STI) or reproductive tract infection (RTI) requiring treatment per current Centers for Disease Control and Prevention (CDC) guidelines (<http://www.cdc.gov/std/treatment/>) at Screening or Enrollment

*Note: Otherwise eligible participants diagnosed with STI or RTI during screening will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 45 days of obtaining informed consent for screening, the participant may be enrolled.*

- 8) At Screening or Enrollment, has a clinically apparent Grade 1 or higher pelvic exam finding (observed by study clinician or designee) per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), Addendum 1, Female Genital Grading Table for Use in Microbicide Studies

*Note: Cervical friability bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the IoR/designee is considered expected non-menstrual bleeding and is not exclusionary.*

- 9) At Screening, severe pelvic relaxation such that either the vaginal walls or the uterine cervix descend beyond the vaginal introitus with valsalva maneuver
- 10) 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 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 vaginal products after the Screening Visit and while taking part in MTN-013/IPM 026. Participation in the following types of studies may be allowed at the discretion of the IoR/designee:

- Participants may take part in ancillary studies approved by MTN-013/IPM 026 Protocol Chair and co-Chair
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-positive persons
- Participants who become pregnant may take part in observational studies, including registries

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-013/IPM 026, the IoR/designee will consult the PSRT regarding ongoing product use and other potential safety considerations associated with co-enrollment.

## **6 STUDY PRODUCT**

### **6.1 Regimen**

Each participant will be randomized to one of four study regimens:

**Table 2: Study Regimen**

<b>Group</b>	<b>N</b>	<b>Group Description</b>
A	12	Dapivirine VR, containing 25 mg dapivirine
B	12	Maraviroc VR, containing 100 mg maraviroc
C	12	Dapivirine + Maraviroc VR, containing 25 mg dapivirine and 100 mg maraviroc
D	12	Placebo VR

Each participant will receive a VR containing either 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc or placebo. The vaginal ring will be worn for approximately 28 consecutive days. It will be inserted into the vagina, by the participant (or clinician if necessary) at the Enrollment Visit and removed by participant (or clinician, if necessary) on Study Visit Day 28. The participant will be followed for an approximately 24 days following ring removal.

## **6.2 Administration**

Study participants will be given detailed instructions in the clinic on proper vaginal ring insertion and removal procedures. Hands should be thoroughly washed before and after study VR insertion and/or removal. Additional details on administration (ring insertion, removal, procedures in the event of expulsion or loss) will be provided in the MTN-013/IPM 026 Study Specific Procedures (SSP) Manual.

## **6.3 Study Product Formulation**

### **6.3.1 Study VR**

The study vaginal ring is an off-white, flexible ring containing drug substance dispersed in a platinum-catalyzed-cured silicone matrix. The drug substance will include either 25 mg of dapivirine, 100 mg of maraviroc, both of these combined or no drug (placebo). The ring dimensions are as follows: 56 mm and 7.7 mm, outer diameter and cross-sectional diameter, respectively. The ring is designed to provide sustained release of drug over a 28-day period.

### **6.3.2 Dapivirine**

Dapivirine 0.3125% (w/w) is dispersed in a flexible, opaque, cured silicone vaginal ring delivery device. The vaginal ring will contain 25 mg of dapivirine.

### **6.3.3 Maraviroc**

Maraviroc 1.25% (w/w) is dispersed in a flexible, opaque, cured silicone vaginal ring delivery device. The vaginal ring will contain 100 mg of maraviroc.

### **6.3.4 Dapivirine/Maraviroc**

The combination ring contains the same active pharmaceutical ingredients as the single agent rings. Dapivirine 0.3125% (w/w) and maraviroc 1.25% (w/w) are dispersed together in a flexible, opaque, cured silicone vaginal ring delivery device. The vaginal ring will contain 25 mg of dapivirine and 100 mg of maraviroc.

### **6.3.5 Placebo**

The placebo vaginal ring is manufactured with the same components as the drug-containing rings, except that it contains USP titanium dioxide dispersed in the silicone fluid as colorant, and no active pharmaceutical ingredient. The purpose of the colorant is for maintaining blinded conditions.

## **6.4 Supply and Accountability**

### **6.4.1 Supply**

IPM (Bethlehem, PA) will manufacture all of the study vaginal rings and analyze/release the rings under Good Manufacturing Practices (GMP). Siris Pharmaceutical Services (Bloomsbury, NJ) will label and ship all study VRs directly to the Pharmacist of Record (PoR) at each study site.

### **6.4.2 Storage and Dispensing**

The vaginal rings should be stored at 15°C to 30°C (59°F to 86°F). Study vaginal rings are dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber.

### **6.4.3 Accountability**

Each site PoR is required to maintain complete records of all study vaginal rings received and subsequently dispensed. All unused study products must be returned to MTN CORE Pharmacist after the study is complete unless otherwise instructed by the MTN CORE Pharmacist. Procedures to be followed will be provided in the MTN-013/IPM 026 Pharmacy Instruction Manual.

## **6.5 Adherence Counseling and Assessment**

Participants will receive study VR adherence counseling at the Enrollment Visit and at additional follow-up visits. Site staff will counsel participants to refrain from removing the ring (except as directed) and from using prohibited medications and practices as described in Section 6.8. Site staff will also provide counseling for re-insertion in case of ring removal/expulsion.

The site staff will counsel participants to remove the vaginal ring immediately and contact study site staff if they experience a rash, itching, or other skin trouble, joint pain, or difficulty breathing as these may be signs of an allergic reaction.

## **6.6 Assessment of Participant Adherence**

Participant behaviors regarding study VR use will be collected via standardized questions developed by the protocol team in conjunction with study site staff and

community representatives, to maximize the accuracy of self-reported data. Assessment of participant adherence will be evaluated using a quantitative instrument.

## **6.7 Concomitant Medications**

Enrolled study participants may use concomitant medications during study participation. All concomitant medications as well as illicit substances reported throughout the course of the study will be recorded on case report forms designated for that purpose. All prescription medications, over-the-counter preparations, vitamins, nutritional supplements, and herbal preparations will be recorded on forms for concomitant medications.

## **6.8 Prohibited Medications and Practices**

Several concomitant medications/practices will not be permitted. Participants are asked to refrain from using CYP3A inhibitors and CYP3A inducers. These medications are not allowed because both dapivirine and maraviroc are CYP3A substrates. Concomitant use of prohibited non-study vaginal products or other devices including but not limited to spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps, douches, lubricants, and sex toys (e.g., vibrators, dildos, etc.) will be assessed. Participants are expected to be sexually abstinent for the duration of study participation, i.e., no receptive intercourse (vaginal, anal, or oral). In addition, tampons also may not be used for the duration of study participation. These medications and practices are restricted in order to protect the integrity of the lower genital tract and reduce the possibility of adverse events due to agents other than the study ring and product.

Participants will be counseled to avoid such use and practices; they will be provided or referred to family planning services for the provision of alternative methods, as applicable.

## 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-013/IPM 026 SSP Manual available at [www.mtnstopshiv.org](http://www.mtnstopshiv.org).

### 7.1 Pre-screening

As part of participant outreach and recruitment strategies, study staff may pre-screen potential study participants at either on-site or off-site locations. During these interactions, study staff may explain the study to potential participants and ascertain elements of presumptive eligibility, to be confirmed at an on-site screening visit. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at the study site in the absence of written informed consent from potential participants, provided the information is collected in such a manner that it cannot be linked to participant identifiers. At each site, procedures and documentation will comply with local IRB requirements.

### 7.2 Screening Visit

Screening may take place up to 45 days prior to Enrollment. Multiple visits may be conducted to complete all required 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.

*NOTE: Women who fail their first screening attempt may be re-screened a maximum of one time.*



**Table 3: Screening Visit**

Screening Visit		
Component	Procedures	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Assign participant ID (PTID)</li> <li>• Obtain written informed consent for screening</li> <li>• Collect demographic information</li> <li>• Assess eligibility (behavioral and clinical)</li> <li>• Collect locator information</li> <li>• Provide reimbursement for study visit</li> <li>• Schedule next visit*</li> </ul>	
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>• Conduct behavioral assessment</li> <li>• Provide counseling                             <ul style="list-style-type: none"> <li>– HIV pre- and post-test</li> <li>– Contraceptive</li> <li>– HIV/STI risk reduction</li> </ul> </li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Collect medical and menstrual history</li> <li>• Collect concomitant medications</li> <li>• Perform physical examination (see Section 7.8)</li> <li>• Perform pelvic examination</li> <li>• Provide available test results</li> <li>• Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Collect urine                             <ul style="list-style-type: none"> <li>– Human Chorionic Gonadotropin (hCG)</li> <li>– Dipstick urinary analysis (UA)</li> <li>– Urine culture*</li> </ul> </li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• Collect blood                             <ul style="list-style-type: none"> <li>– HIV-1 serology</li> <li>– Syphilis serology</li> <li>– Complete blood count (CBC) with differential and platelets</li> <li>– Chemistries</li> </ul> </li> </ul>
	<b>Vaginal</b>	<ul style="list-style-type: none"> <li>• Collect pelvic specimens                             <ul style="list-style-type: none"> <li>– Rapid test for Trichomonas</li> <li>– Nucleic Acid Amplification Test (NAAT) for <i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i> (GC/CT)</li> <li>– Vaginal fluid pH*</li> <li>– Potassium hydroxide (KOH) wet mount for candidiasis*</li> <li>– Saline wet mount for bacterial vaginosis (BV)*</li> </ul> </li> </ul>
	<b>Cervical</b>	<ul style="list-style-type: none"> <li>• Pap smear interpretation*</li> </ul>

\* If indicated

### 7.3 Enrollment Visit (Day 0)

**Table 4: Enrollment Visit**

Enrollment Visit		
Component	Procedures	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Obtain written informed consent for enrollment and specimen storage and possible future research testing</li> <li>• Assess consent form comprehension</li> <li>• Confirm eligibility (behavioral and clinical)</li> <li>• Review/update locator information</li> <li>• Randomization</li> <li>• Provide reimbursement for study visit</li> <li>• Schedule next visit*</li> </ul>	
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>• Conduct behavioral assessment</li> <li>• Provide counseling               <ul style="list-style-type: none"> <li>– HIV pre- and post-test</li> <li>– Contraceptive</li> <li>– Protocol adherence</li> <li>– Product use/adherence</li> <li>– HIV/STI risk reduction</li> </ul> </li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical and menstrual history</li> <li>• Review/update concomitant medications</li> <li>• Document pre-existing conditions</li> <li>• Perform physical examination</li> <li>• Perform pelvic examination               <ul style="list-style-type: none"> <li>– Visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004)</li> </ul> </li> <li>• Provide available test results</li> <li>• Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Collect urine               <ul style="list-style-type: none"> <li>– hCG</li> <li>– Dipstick UA*</li> <li>– Urine culture*</li> </ul> </li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• Collect blood               <ul style="list-style-type: none"> <li>– HIV-1 serology</li> <li>– CBC with differential and platelets</li> <li>– Chemistries</li> <li>– Plasma archive</li> <li>– PK (Post ring insertion at time points: hrs 0, 1, 2, 4, 6)</li> </ul> </li> </ul>
	<b>Vaginal</b>	<ul style="list-style-type: none"> <li>• Collect pelvic specimens               <ul style="list-style-type: none"> <li>– Vaginal pH</li> <li>– Gram stain</li> <li>– Vaginal swab for vaginal biomarker assessment and pharmacodynamics (PD)</li> <li>– Quantitative vaginal culture</li> <li>– Tear test strip</li> <li>– KOH wet mount for candidiasis*</li> <li>– Saline wet mount for BV*</li> <li>– Rapid test for Trichomonas*</li> <li>– NAAT for GC/CT*</li> </ul> </li> </ul>
<b>Study Product Supply</b>		<ul style="list-style-type: none"> <li>• Participants will receive study VR, study VR use instructions and will be instructed to self-insert the study VR, followed by pelvic exam to check placement</li> </ul>

\* If indicated

## 7.4 Follow-up Visits

The following procedures will occur on Days 1, 2, 3, 5, 7, 14, 21, 28, 29, 30, 31, 35, 42, and Day 52/Final Clinic or Early Termination Visit.

### 7.4.1 Visit Days 1, 2, 3, 5, 7, 14, 21

Table 5: Visit Days 1, 2, 3, 5, 7, 14, 21

Component		Procedures
<b>Administrative and Regulatory</b>		<ul style="list-style-type: none"> <li>Review/update locator information</li> <li>Provide reimbursement for study visit</li> <li>Record/update AEs</li> <li>Schedule next visit</li> </ul>
<b>Behavioral</b>		<ul style="list-style-type: none"> <li>Conduct adherence assessment☼</li> <li>Provide modified counseling               <ul style="list-style-type: none"> <li>Contraceptive</li> <li>Protocol adherence</li> <li>Product use/adherence</li> <li>HIV/STI risk reduction</li> </ul> </li> </ul>
<b>Clinical</b>		<ul style="list-style-type: none"> <li>Review/update medical and menstrual history</li> <li>Review/update concomitant medications</li> <li>Perform physical examination</li> <li>Perform pelvic examination               <ul style="list-style-type: none"> <li>Visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004</li> </ul> </li> <li>Provide available test results</li> <li>Treat for UTIs/RTIs/STIs or refer for other findings*</li> </ul>
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>Collect urine*               <ul style="list-style-type: none"> <li>hCG☼*</li> <li>Dipstick UA*</li> <li>Urine culture*</li> </ul> </li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>Collect blood               <ul style="list-style-type: none"> <li>PK (single time point)</li> </ul> </li> </ul>
	<b>Vaginal</b>	<ul style="list-style-type: none"> <li>Collect pelvic specimens               <ul style="list-style-type: none"> <li>Tear test strip</li> <li>Vaginal pH♦ *</li> <li>Gram Stain♦</li> <li>Vaginal biomarkers♦</li> <li>Quantitative vaginal culture◊</li> <li>KOH wet mount for candidiasis*</li> <li>Saline wet mount for BV*</li> <li>Rapid test for Trichomonas*</li> <li>NAAT for GC/CT*</li> </ul> </li> </ul>

\* If indicated ♦ Day 3 only, ☼Day 7, Day 14, and Day 21 visits only, ☼ Day 14 only, ◊ Day 7 only

## 7.4.2 Visit Day 28, Ring Removal Visit

The following procedures will occur at Visit Day 28 or the Ring Removal Visit.

**Table 6: Visit Day 28: Ring Removal Visit**

Follow-up Visit: Day 28		
Component	Procedures	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Review/update locator information</li> <li>• Provide reimbursement</li> <li>• Record/update AEs</li> <li>• Schedule next visit</li> </ul>	
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>• Conduct behavioral assessment</li> <li>• Conduct adherence assessments</li> <li>• Conduct a face-to-face interview</li> <li>• Provide counseling               <ul style="list-style-type: none"> <li>– Contraceptive</li> <li>– Protocol adherence</li> <li>– HIV/STI risk reduction</li> <li>– HIV pre- and post-test*</li> </ul> </li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical and menstrual history</li> <li>• Review/update concomitant medications</li> <li>• Perform physical examination</li> <li>• Perform pelvic examination               <ul style="list-style-type: none"> <li>– Visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004</li> </ul> </li> <li>• Provide available test results</li> <li>• Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Collect urine               <ul style="list-style-type: none"> <li>– hCG</li> <li>– Dipstick UA*</li> <li>– Urine culture*</li> </ul> </li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• Collect blood               <ul style="list-style-type: none"> <li>– PK (Post ring removal at time points: hrs 0, 1, 2, 4, 6)</li> <li>– CBC with differential and platelets</li> <li>– Chemistries</li> <li>– HIV-1 serology*</li> </ul> </li> </ul>
	<b>Vaginal</b>	<ul style="list-style-type: none"> <li>• Collect pelvic specimens               <ul style="list-style-type: none"> <li>– Vaginal pH</li> <li>– Gram stain</li> <li>– Vaginal swab for vaginal biomarker assessment and PD</li> <li>– Quantitative vaginal culture</li> <li>– Tear test strip</li> <li>– KOH wet mount for candidiasis*</li> <li>– Saline wet mount for BV*</li> <li>– Rapid test for Trichomonas*</li> <li>– NAAT for GC/CT*</li> </ul> </li> <li>• Designated site(s) only: a biofilm assessment and/or residual levels of dapivirine and/or maraviroc will be assessed on returned vaginal rings if the rings are removed in accordance with VR assessment criteria, see SSP.               <ul style="list-style-type: none"> <li>– <i>Note: In the event that the study VR is removed at an earlier visit, the used ring may have a biofilm assessment and/or residual level of dapivirine and/or maraviroc analysis if VR assessment criteria are met, see SSP.</i></li> </ul> </li> </ul>
	<b>Cervical</b>	<ul style="list-style-type: none"> <li>• Cervical tissue biopsy for PK and PD</li> </ul>
<b>Study Product</b>	<ul style="list-style-type: none"> <li>• Collect used VR</li> </ul>	

\* if indicated

### 7.4.3 Visit Days 29 and 30

The following procedures will occur at Visit Days 29 and 30.

**Table 7: Visit Days 29 and 30**

<b>Follow-up Visits: Days 29 and 30</b>		
<b>Component</b>	<b>Procedures</b>	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Review/update locator information</li> <li>• Provide reimbursement for study visit</li> <li>• Record/update AEs</li> <li>• Schedule next visit</li> </ul>	
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>• Provide modified counseling               <ul style="list-style-type: none"> <li>– Contraceptive</li> <li>– Protocol adherence</li> <li>– HIV/STI risk reduction</li> </ul> </li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical and menstrual history</li> <li>• Review/update concomitant medications</li> <li>• Perform physical examination</li> <li>• Perform pelvic examination*               <ul style="list-style-type: none"> <li>– Visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004</li> </ul> </li> <li>• Provide available test results</li> <li>• Treat for UTIs/RTIs/STIs or refer for other findings*</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Collect urine*               <ul style="list-style-type: none"> <li>– hCG*</li> <li>– Dipstick UA*</li> <li>– Urine culture*</li> </ul> </li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• Collect blood               <ul style="list-style-type: none"> <li>– PK (single time point)</li> </ul> </li> </ul>
	<b>Vaginal</b>	<ul style="list-style-type: none"> <li>• Collect pelvic specimens*               <ul style="list-style-type: none"> <li>– Vaginal pH*</li> <li>– KOH wet mount for candidiasis*</li> <li>– Saline wet mount for BV*</li> <li>– Rapid test for Trichomonas*</li> <li>– NAAT for GC/CT*</li> </ul> </li> </ul>

\* If indicated

#### 7.4.4 Visit Days 31, 35, 42

The following procedures will occur at Visit Days 31, 35, and 42.

**Table 8: Visit Days 31, 35, 42**

Follow-up Visits: Days 31, 35, 42		
Component	Procedures	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Review/update locator information</li> <li>• Provide reimbursement for study visit</li> <li>• Record/update AEs</li> <li>• Schedule next visit</li> </ul>	
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>• Provide modified counseling               <ul style="list-style-type: none"> <li>– Contraceptive</li> <li>– Protocol adherence</li> <li>– HIV/STI risk reduction</li> <li>– HIV pre- and post-test*</li> </ul> </li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical and menstrual history</li> <li>• Review/update concomitant medications</li> <li>• Perform pelvic examination †               <ul style="list-style-type: none"> <li>– Visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004</li> </ul> </li> <li>• Perform physical examination</li> <li>• Disclosure of available test results</li> <li>• Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Collect urine †*               <ul style="list-style-type: none"> <li>– hCG †*</li> <li>– Dipstick UA*</li> <li>– Urine culture*</li> </ul> </li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• Collect blood               <ul style="list-style-type: none"> <li>– HIV-1 serology*</li> <li>– PK (single time point)</li> </ul> </li> </ul>
	<b>Vaginal</b>	<ul style="list-style-type: none"> <li>• Collect pelvic specimens †*               <ul style="list-style-type: none"> <li>– Vaginal pH ■</li> <li>– Tear test strip †</li> <li>– Vaginal swab for vaginal biomarker assessment and PD ■</li> <li>– Gram stain ■</li> <li>– KOH wet mount for candidiasis*</li> <li>– Saline wet mount for BV*</li> <li>– Rapid test for Trichomonas*</li> <li>– NAAT for GC/CT*</li> </ul> </li> </ul>
	<b>Cervical</b>	<ul style="list-style-type: none"> <li>• Cervical tissue biopsy for PK †</li> </ul>

\* If indicated, † To be completed on Day 31, 35, or 42 based upon randomization assignment, ■ Day 31 only

## 7.4.5 Visit Day 52, Final Clinic/Early Termination Visit

Table 9: Visit Day 52, Final Clinic/Early Termination Visit

Final Clinic/ Early Termination Visit: Visit Day 52		
Component	Procedures	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Review/update locator information</li> <li>• Provide reimbursement for study visit</li> <li>• Record/update AEs</li> <li>• Schedule next visit*</li> </ul>	
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>• Conduct behavioral assessment</li> <li>• Conduct adherence assessment▲</li> <li>• Provide counseling               <ul style="list-style-type: none"> <li>– HIV/STI risk reduction</li> <li>– HIV pre- and post-test</li> </ul> </li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical and menstrual history</li> <li>• Review/update concomitant medications</li> <li>• Perform pelvic examination               <ul style="list-style-type: none"> <li>– Visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004</li> </ul> </li> <li>• Perform physical examination</li> <li>• Disclosure of available test results</li> <li>• Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Collect urine               <ul style="list-style-type: none"> <li>– hCG</li> </ul> </li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• Collect blood               <ul style="list-style-type: none"> <li>– Chemistries</li> <li>– CBC with differential and platelets</li> <li>– PK (single time point)</li> <li>– HIV-1 serology</li> </ul> </li> </ul>
	<b>Vaginal</b>	<ul style="list-style-type: none"> <li>• Collect pelvic specimens               <ul style="list-style-type: none"> <li>– Vaginal biomarkers</li> <li>– Gram stain</li> <li>– Vaginal pH</li> <li>– Tear test strip</li> <li>– Quantitative vaginal culture</li> <li>– KOH wet mount for candidiasis*</li> <li>– Saline wet mount for BV*</li> <li>– Rapid test for Trichomonas*</li> <li>– NAAT for GC/CT*</li> </ul> </li> </ul>
<b>Study Product</b>	<ul style="list-style-type: none"> <li>• Provision of condoms*</li> <li>• Collect VR▲</li> </ul>	

\* If indicated, ▲ If Early Termination Visit and not already performed

## 7.5 Follow-up Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product

### 7.5.1 Participants Who Become Infected with HIV-1

Participants who become infected with HIV-1 will be referred for treatment according to the local standard of care. Participants will be permanently discontinued from VR use and will be instructed to return the study VR. HIV RNA and HIV drug resistance testing will be done. Study staff, with written permission from the participant, may contact the medical care provider to inform him/her of the participant's involvement in MTN-013/IPM 026. The participant will be offered the option to continue follow-up visits per their original study schedule until their originally scheduled study exit date. For those who

choose to remain in follow-up, protocol-specified procedures will continue except the following:

- HIV-1 serology
- Provision of study product
- Acceptability and adherence assessments
- Pelvic exams
- PK specimen collection (blood and pelvic samples)
- Provision of counseling
  - HIV pre- and post-test
  - Protocol and product use adherence

HIV/STI risk reduction counseling will be modified to address primary and secondary prevention for infected women.

### **7.5.2 Participants Who Become Pregnant**

Participants will be permanently discontinued from VR use and will be instructed to return the study VR. All protocol-specified study procedures will continue except the following:

- Urine hCG testing
- Provision of study product
- Acceptability and adherence assessments
- Pelvic exams
- PK specimen collection (blood and pelvic specimens)
- Provision of counseling
  - Contraceptive
  - Product adherence

Participants who become pregnant while on study may be offered enrollment in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study, ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)), provided their study site is participating in MTN-016. In the event that a study site is not activated for MTN-016, participants may be contacted to collect the outcome of pregnancies up to one year after the birth of the infant.

A participant who is pregnant at the Final Clinic/Early Termination Visit (Day 52) will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained).

### **7.5.3 Participants Who Permanently Discontinue Study Product Use (Participant Volunteer or IoR Discretion)**

Participants who are permanently discontinued from VR use will be instructed to return the study VR. All protocol-specified study procedures will continue except the following:



- Provision of study product
- Pelvic exams\*
- PK specimen collection
- Provision of adherence counseling
- Acceptability and adherence assessments

\*Unless required for AE follow-up

#### 7.5.4 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 CRFs.

**Table 10: Interim Visit(s)**

Component		Interim Visit(s) Procedures
<b>Administrative and Regulatory</b>		<ul style="list-style-type: none"> <li>• Review/update locator information*</li> <li>• Provide reimbursement*</li> <li>• Schedule next visit*</li> <li>• Record/update AEs</li> </ul>
<b>Behavioral</b>		<ul style="list-style-type: none"> <li>• Provide counseling* <ul style="list-style-type: none"> <li>– HIV/STI risk reduction*</li> <li>– Contraceptive*</li> <li>– Protocol adherence*</li> <li>– Product use adherence*</li> <li>– HIV pre-and post-test*</li> </ul> </li> </ul>
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Review/update medical and menstrual history*</li> <li>• Review/update concomitant medications*</li> <li>• Perform pelvic examination*</li> <li>• Perform physical exam*</li> <li>• Disclosure of available test results</li> <li>• Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*</li> </ul>
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Collect urine* <ul style="list-style-type: none"> <li>– hCG*</li> <li>– Dipstick UA*</li> <li>– Urine culture*</li> </ul> </li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• Collect blood* <ul style="list-style-type: none"> <li>– HIV-1 serology*</li> <li>– Chemistries*</li> <li>– CBC with differential and platelets*</li> <li>– Syphilis serology*</li> </ul> </li> </ul>
	<b>Vaginal</b>	<ul style="list-style-type: none"> <li>• Collect pelvic samples* <ul style="list-style-type: none"> <li>– Vaginal pH*</li> <li>– KOH wet mount for candidiasis*</li> <li>– Saline wet mount for BV*</li> <li>– Rapid test for Trichomonas*</li> <li>– NAAT for GC/CT*</li> </ul> </li> </ul>
<b>Study Product</b>		<ul style="list-style-type: none"> <li>• Collect VR*</li> </ul>

\* if indicated

## 7.6 Pharmacokinetics

All enrolled participants will undergo PK specimen collection procedures. These PK specimen collections will occur at study visits as described in the table below. Blood, tear test strips, and cervical biopsies will be collected to assay for dapivirine and maraviroc concentrations.

Blood and pelvic PK specimens should be collected within approximately one hour of each other in the sequence listed above, if a single time point collection is planned. Participants will report ring adherence, including the reason for ring expulsion or removal as well as the date and approximate length of time that the ring was out of the vagina. Study staff will record this information. In addition, women will also be asked questions via CASI regarding vaginal and other practices (e.g., sex, tampon use, etc.) in an effort to further inform the PK analysis. These data may be collected at study visits in which PK assessments are scheduled to occur, see Table 11 below. Staff will also record all PK specimen collection times.

In order to maintain the critical double-blind design element in this protocol, the collection of the samples described above is also necessary in VR placebo recipients. Sampling of a placebo group is a routine occurrence in drug development protocols, including no benefit phase I protocols in healthy volunteers. These samples will contribute to the quality of all study data by maintaining the integrity of the double-blind study design.

**Table 11: PK Specimen Collection Schedule**

STUDY VISIT		PK Specimen Collection
Screening		None
Enrollment		Blood (hr 0, 1, 2, 4, 6), Tear test strip
Day 1		Blood, Tear test strip
Day 2		Blood, Tear test strip
Day 3		Blood, Tear test strip
Day 5		Blood, Tear test strip
Day 7		Blood, Tear test strip
Day 14		Blood, Tear test strip
Day 21		Blood, Tear test strip
Day 28		Blood (hr 0, 1, 2, 4, 6) Tear test strip , Cervical tissue
Day 29		Blood
Day 30		Blood
Participants will be randomized to undergo Tear test strip and cervical tissue PK collection on Day 31, 35, or 42	Day 31	Blood, Tear test strip <sup>‡</sup> , Cervical tissue <sup>‡</sup>
	Day 35	Blood, Tear test strip <sup>‡</sup> , Cervical tissue <sup>‡</sup>
	Day 42	Blood, Tear test strip <sup>‡</sup> , Cervical tissue <sup>‡</sup>
Day 52		Blood, Tear test strip

<sup>‡</sup> 1/3 of the group, as designated by PK randomization

## 7.7 Behavioral Measures

The primary behavioral study aims will be addressed using a quantitative instrument and an in-depth qualitative interview (conducted at Day 28).

The quantitative instrument will be structured around the following topics:

- Product acceptability
- Product adherence (VR use)
- Protocol adherence (including sexual activity)

Participants will be asked to complete an in-depth qualitative interview that addresses use of study product during the trial. This interview will be conducted by a trained study interviewer and will follow a structured interview guide. Participants will be asked about their experience with the ring, change in feelings about the ring, concerns, worries about wearing the ring for 28 days, and explorations of the context around ring removal/expulsion. They will be approximately 30 minutes in duration and will be conducted at the 28-Day study visit and modeled off the Gel Use Experience form developed for MTN-008.

### 7.7.1 Acceptability

Acceptability will be measured via questions about product and user-related attributes, such as ease of insertion and removal, genitourinary discomfort, awareness/feeling the study VR during daily activities, emotional comfort wearing the ring continuously for 28 days, and willingness to use an HIV protective ring in the future, if one were available. This quantitative assessment will be modeled off of the acceptability assessment planned for Protocol MTN-005 ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)) and used in IPM 009 (<http://www.ipmglobal.org/>).

### 7.7.2 Adherence

Key adherence measures will be captured by Computer-Assisted Self Interviewing (CASI) and by CRFs to ensure maximum confidentiality of responses. The questions will assess study VR use, report of frequency of study VR removal/expulsions (voluntary and involuntary) and duration without VR inserted in vagina. A series of questions will ask if the study VR was out, whether it was removed or expelled, under what circumstances or conditions it was removed or expelled, and whether it was re-inserted. A combination of self-administered and interviewer-administered questionnaires will be employed to capture the above information. Study staff will provide participants with guidance on strategies to optimize recall of relevant behavioral and adherence data. This quantitative assessment will be modeled off of the adherence assessment planned for Protocol MTN-005 ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)) and used in IPM 009 (<http://www.ipmglobal.org/>).

## 7.8 Clinical Evaluations and Procedures

Physical exams will include the following assessments:

- General appearance
- Weight
- Vital signs
  - Temperature
  - Pulse
  - Blood pressure
  - Respirations
- Height \*
- Abdomen\*
- Head, Eye, Ear, Nose and Throat (HEENT) Examination\*
- Lymph nodes\*
- Neck\*
- Heart\*
- Lungs\*
- Extremities\*
- Skin\*
- Neurological\*

\*may be omitted after the Enrollment Visit

Additional clinical assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam.

Pelvic exams will be conducted per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at <http://www.conrad.org/publications-13.html>. The required sequence of procedures and specimen collection performed during pelvic exams will be specified in the MTN-013/IPM 026 SSP Manual.

## 7.9 Laboratory Evaluations

### Local Laboratory

- Urine
  - hCG
  - Dipstick UA
  - Urine culture

- Blood
  - Plasma archive
  - Syphilis
  - HIV serology
  - CBC with differential and platelets
  - Chemistries
    - Creatinine
    - AST
    - ALT
- Vaginal
  - pH
  - Rapid test for Trichomonas
  - Saline wet mount for BV
  - KOH wet mount for candidiasis
  - Chlamydia and gonorrhea
- Cervical
  - Pap smear interpretation

#### Network Laboratory

- Blood
  - Standardized and specialized HIV-1 resistance tests
- Vaginal
  - Gram stain assessment of vaginal fluid slides
  - Tear test strip for anti-viral activity
  - Biomarker assessment of vaginal swab
  - Biopsy for PK assessment
  - Fluid for PD assessment
  - Biofilm assessment of used study VRs (at designated site(s) only)
- Cervical
  - Biopsy for PD assessment
- Blood/vaginal/cervical samples dapivirine and maraviroc levels (NL Pharmacology Core)

#### IPM Designated Laboratory

- Vaginal
  - Used study VR residual drug level assessment (at designated site(s) only)

### **7.10 Specimen Collection and Processing**

Each study site will adhere to the standards of good clinical laboratory practice, the MTN Network Laboratory Manual ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)), in accordance with current DAIDS Laboratory Requirements, MTN-013/IPM 026 Study Specific Procedures Manual

([www.mtnstopshiv.org](http://www.mtnstopshiv.org)), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

### **7.11 Specimen Handling**

Specimens will be handled in accordance with current requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials. (<http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/labpolicy.pdf>)

### **7.12 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 National Institutes of Health (NIH). All biological specimens will be transported using packaging mandated by Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

## **8 ASSESSMENT OF SAFETY**

### **8.1 Safety Monitoring**

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 Medical Officer, Protocol Safety Physicians, IPM Safety Physicians, and SCHARP Clinical Affairs Safety Associates will serve as the PSRT. The MTN Statistical Data Management Center (SDMC) prepares routine AE and clinical data reports (blinded to treatment assignment) for review by the PSRT, which meets via conference call approximately once per month 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. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise. Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC Clinical Affairs staff, the PSRT and study sponsors. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

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. If necessary, experts external to the MTN representing expertise in the fields of microbicides, biostatistics, HIV transmission and medical ethics may be invited to join the PSRT safety review. A recommendation to pause or stop 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 in all participants, IPM will notify the FDA and the Clinical Research Site (CRS) 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 and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition is applied to all study groups, and is applied to all groups beginning at the time of enrollment (i.e., once a participant is

assigned a study randomization envelope). The term “investigational product” for this study refers to all study products.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience. In cases of potentially life-threatening events, participants will be 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 site staff will document in source documents and the appropriate AE Log CRF all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. 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) and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009)), except that asymptomatic BV and asymptomatic candidiasis will not be reportable AEs. In cases where a genital AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

### **8.3.2 Serious Adverse Events**

SAEs 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 event that may not result in death, be immediately life-threatening, or require hospitalization but may jeopardize the participant or require 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. Per 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 Expedited Adverse Event Reporting Requirements**

### **8.4.1 Adverse Event Reporting to DAIDS**

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS Expedited Adverse Event (EAE) 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](mailto: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](mailto: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 VR, maraviroc VR, dapivirine/maraviroc VR, placebo VR.

### **8.4.3 Grading Severity of Events**

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, Dec 2004 (clarification dated August 2009), and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004, clarification dated August 2009) will be used and are 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 at enrollment (i.e., once a participant is assigned a study randomization envelope) 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 Pregnancy and Pregnancy Outcomes**

Pregnant women are excluded from this study. If participants become pregnant at any time during the course of the study, participants will remain in the study and procedures will be conducted as per study protocol, see Section 7.5.2.

Pregnancy-related data will be collected using pregnancy CRFs for all pregnancies detected during the study. Pregnancy outcomes will not be expeditiously reported to IPM or the DAIDS Medical Officer (MO) unless there is an associated AE in the pregnant participant that meets expedited reporting criteria or the pregnancy results in a congenital anomaly meeting the Manual for Expedited Reporting of EAEs to DAIDS (Version 2.0, January 2010) guidelines for expedited reporting.

#### **8.6 Regulatory Requirements**

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

#### **8.7 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 IIR/designee to be serious or unexpected will be reported to the PSRT and responsible site IRBs according to their individual requirements.

## **9 CLINICAL MANAGEMENT**

Guidelines for clinical management and temporary product hold/permanent discontinuation of study product are outlined in this section. In general, the

IoR/designee has the discretion to hold study product temporarily at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. Unless otherwise specified below, the IoR/designee should immediately consult the PSRT for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs.

## **9.1 Grading System**

AE severity grading is described in Section 8.3.1.

## **9.2 Dose Modification Instructions**

No dose modifications will be undertaken in this study.

## **9.3 General Criteria for Temporary Hold and Permanent Discontinuation of Study Product**

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

- Acquisition of HIV-1 infection; study product should be held beginning immediately upon recognition of the first reactive rapid HIV test (permanent discontinuation)
- Pregnancy (permanent discontinuation)
- Breastfeeding (permanent discontinuation)
- Report of use of post-exposure prophylaxis (PEP) for HIV exposure (permanent discontinuation)
- Report of use of prohibited medications described in 6.8; product use may resume when the participant reports no longer taking the prohibited medication, provided other reasons for temporary product hold/permanent discontinuation do not apply
- 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.
  - The IoR/designee must consult the PSRT on all temporary product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation.

- If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time.

## **9.4 Temporary Product Hold/Permanent Discontinuation in Response to Adverse Events**

### **Grade 1 or 2**

In general, a participant who develops a Grade 1 or 2 AE as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and the Female Genital Grading Table for Use in Microbicide Studies, Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) regardless of relationship to study product that is not specifically addressed in Section 9.5 below may continue product use. If the IoR/designee opts to temporarily hold study product, the PSRT must be notified.

### **Grade 3**

Participants who develop a Grade 3 AE as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and the Female Genital Grading Table for Use in Microbicide Studies, Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) that is not specifically addressed in Section 9.5 and judged by the IoR/designee to be unrelated to study product may continue product use. If the IoR/designee opts to hold study product, the PSRT must be notified.

For participants who develop a Grade 3 AE that is not specifically addressed in Section 9.5 that is judged by the IoR/designee to be related to product, the PSRT must be consulted to determine if the participant may continue to use product. The IoR/designee will determine whether a temporary product hold is required while awaiting a decision from the PSRT. Assuming product use continues the IoR/designee must follow-up within 72 hours on this event (unless a different management plan has been devised in consultation with the PSRT).

If a recurrence of the same Grade 3 AE judged to be related to study product recurs at any time during the study, the IoR/designee must permanently discontinue study product.

### **Grade 4**

A participant who develops a Grade 4 AE as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and the Female Genital Grading Table for Use in Microbicide Studies, Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) that is not specifically

addressed in Section 9.5 that is judged by the IoR/designee to be unrelated to study product should have the study product temporarily held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT. If, in consultation with the PSRT, product use is resumed and the same AE recurs regardless of relationship to study product, at a Grade 4 level at any time during the study, study product must then be permanently discontinued.

Participants who develop a Grade 4 AE that is not specifically addressed in Section 9.5 and is judged by the IoR/designee to be related to product should have the study product permanently discontinued.

## **9.5 Other Clinical Events**

Management of sexually transmitted infections commonly referred to as STIs and other forms of vaginitis and cervicitis will be in accordance with current CDC guidelines (<http://www.cdc.gov/std/treatment/>). When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible to avoid intravaginal medication use.

In the absence of clinical evidence of cervicitis (as described below) and/or pelvic inflammatory disease, participants with gonorrhea and/or chlamydia detected during study period may be treated with the study VR in place.

If suspected finding is reported by participant between scheduled visits, an interim visit may be scheduled at the discretion of the site investigator. Management of genital events observed at scheduled or interim visits will be in accordance with the following:

### **Superficial epithelial disruption (abrasion/peeling)**

- Continue study VR use
- Perform naked eye evaluation
- Re-evaluate by speculum examination in 48-72 hours
- If condition worsens, temporarily hold study VR use and consult the PSRT. Otherwise continue study VR use

### **Deep epithelial disruption (ulceration)**

- Remove study VR for deep epithelial disruption confirmed by site investigator
- Re-evaluate in 48-72 hours and reinstate study VR use if resolved
- If unresolved at 48-72 hours, re-evaluate in another 48-72 hours. If resolved at that time, may reinstate study VR use. If unresolved at this second reevaluation, continue temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard
- If there is reoccurrence with no identified etiology, continue temporary product hold and consult the PSRT regarding permanent discontinuation

**Localized erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface**

- Continue study VR use
- Perform naked eye evaluation
- If asymptomatic, re-evaluate at next regularly scheduled visit
- If symptomatic, re-evaluate by speculum examination in 48-72 hours
- If worsened significantly, temporarily hold study VR use and consult the PSRT. Otherwise, continue study VR use

**Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema**

- Remove study VR
- Perform naked eye evaluation
- Re-evaluate in 48-72 hours and reinstate study VR use if resolved
- If unresolved at 48-72 hours, re-evaluate in another 48-72 hours. If resolved at that time may reinstate use. If unresolved at this second reevaluation, continue temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard

**Abnormal vaginal discharge (judged to be unrelated to cervicitis)**

- Study VR use may be continued without treatment in the presence of asymptomatic Candida vaginitis and/or asymptomatic BV
- Perform vaginitis evaluation, including assessment of signs, symptoms, vaginal pH and wet mount microscopy for Candida vaginitis, Trichomoniasis, and BV
- Provide or prescribe treatment and continue study VR use for all cases of Trichomoniasis, symptomatic Candida vaginitis, and symptomatic BV

**Unexpected genital bleeding**

- Continue study VR use (at study clinician's discretion)
- Perform naked eye evaluation
- If determined to be due to deep epithelial disruption, refer to guidelines above, otherwise continue study VR use

**Cervicitis (including findings on exam such as inflammation and/or friability)**

- Remove study VR
- Evaluate for GC/CT
- If GC/CT detected, provide or prescribe treatment and consult PSRT
- If GC/CT is not detected, reevaluate in 72 hours. If all symptoms and signs are resolved at that time continue study VR use

**Genital petechia(e)**

- Continue study VR use
- Perform naked eye evaluation
- No further evaluation or treatment is required

### **Genital ecchymosis**

- Continue study VR use
- Perform naked eye evaluation
- No further evaluation or treatment is required

### **9.6 HIV-1 Infection**

A participant who has a positive test for HIV-1 must have study product held. If the HIV-1 infection is confirmed, based upon the algorithm in Appendix II, study product will be permanently discontinued.

### **9.7 Pregnancy**

All study participants are required to be sexually abstinent during MTN-013/IPM 026.

Pregnancy testing will be performed at scheduled study visits and participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The IoR/designee will counsel any participant who becomes pregnant regarding possible risks to the fetus according to site SOPs. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Pregnancy outcomes will be reported on relevant CRFs; outcomes meeting criteria for EAE reporting also will be reported on EAE forms.

A participant who becomes pregnant during the course of study participation may be offered participation in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study, at sites participating in MTN-016. This registry study captures pregnancy outcomes as well as infant health information, (including growth and development), to evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy. In the event that a study site is not taking part in MTN-016, participants may be contacted to collect the outcome of pregnancies up to one year after the birth of the infant.

Participants who become pregnant during the course of the study will permanently discontinue study product use but will not routinely be withdrawn from the study. Rather, if the participant does not withdraw her consent, every effort will be made to complete all study visits.

## 9.8 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The IIR/designee 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 IPM, NIAID, MTN, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume product use (if applicable) and follow-up through their originally scheduled study exit date, pending consultation with the PSRT.

## 10 STATISTICAL CONSIDERATIONS

### 10.1 Overview and Summary of Design

This is a multi-site, double-blinded, four arm, 1:1:1:1 randomized, placebo-controlled trial to assess and compare the safety and PK of VRs containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc, when used continuously for 28 days by healthy, HIV-uninfected, sexually abstinent women, as compared with a placebo VR. A total of approximately 48 women (12 in each arm) will be randomized.

### 10.2 Study Endpoints

#### Primary endpoints

Consistent with the primary study objective to assess and compare the safety of VRs containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc, when used continuously for 28 days by healthy, HIV-uninfected, sexually abstinent women, as compared with a placebo VR, the primary safety endpoints are the proportion of women in each of the four VR regimens with:

- Evidence of a Grade 1 or higher genitourinary events as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009), Addendum 1, (Female Genital Grading Table for use in Microbicide Studies) during the trial period judged to be related to study product.
- Evidence of Grade 2 or higher adverse events as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009) during the trial period



Consistent with the primary study objective to examine systemic and local pharmacokinetics of dapivirine and maraviroc in vaginal fluids, plasma, and cervical tissue during and after 28 days continuous use of a matrix vaginal ring containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc the pharmacokinetic endpoints will be:

- Assessments of systemic and local concentrations of dapivirine and maraviroc in plasma and vaginal fluids, and cervical tissue, respectively.

### **Secondary endpoints**

Consistent with the secondary objective to evaluate the acceptability of the study VR in HIV-uninfected sexually abstinent women, the following endpoint will be assessed:

- Participant report of acceptability including genitourinary and emotional (dis)comfort, awareness/feeling during daily activities, ring insertion/removal issues, and willingness to use in the future

Consistent with the secondary objective to evaluate the adherence to the study VR in HIV-uninfected sexually abstinent women, the following endpoint will be assessed:

- Participant report of frequency of study VR removal/expulsions (voluntary and involuntary) and duration without VR inserted in vagina

### **Exploratory endpoints**

- Measures of HIV-1 inhibition by mucosal secretions and within cervical tissue
- Abnormal vaginal flora as assessed by Gram stain
- Presence of candidate biomarkers of safety and efficacy in mucosal secretions
- Presence of biofilms on study VR surface
- Dapivirine and maraviroc levels measured in returned VR
- Participant report of duration without VR inserted in vagina

## **10.3 Primary Study Hypothesis**

MTN 013 hypothesizes that the VRs containing dapivirine and/or maraviroc will be as safe and as well-tolerated as the VR containing placebo.

## **10.4 Sample Size and Power Calculations**

### **10.4.1 Safety Endpoints**

The proposed total sample size is approximately N=48 women randomized into 4 arms in a 1:1:1:1 ratio giving 12 women per group. This sample size is based upon the size of similar Phase 1 studies of vaginal microbicide products.

As a means to characterize the statistical properties of this study the table below presents the probability of observing zero, at least one, and two or more safety endpoints among the 12 women in each group for various “true” event rates:

**Table 12: Analysis of Safety Event Frequency**

Event Rate	P (0 events   n=12)	P ( $\geq 1$ event   n=12)	P ( $\geq 2$ 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

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 a particular arm of the study is 26.4%.

**Table 13: Exact 2-sided 95% Confidence Intervals Based on Observing a Particular Rate of Safety Endpoints for Arms of Size 12**

Observed event rate	Confidence interval (%)
0/12	0,26.4
1/12	.21,38.4
2/12	2.1,48.4

An additional aim of the study is to compare the safety between each of the drug containing VR arms of the study and the placebo VR. Assuming a one-sided test with  $\alpha=0.05$  and 90% power, the table below provides the difference in the rates of safety events (proportion of women experiencing the safety event of interest) between a drug containing VR arm and the placebo VR arm that is detectable with 90% power for a given rate in the placebo VR arm. For example, if the true rate of a given toxicity endpoint in the placebo VR arm is 16.7% (2 of 12 women experiencing a safety event), the proposed sample size provides 90% power to exclude safety endpoint rates greater than 79.0% (72.6% with 80% power). Hence, while comparisons will be made between the drug containing VR arms of the study and the placebo VR arm, the study will only have power to detect very large differences in safety event rates.

**Table 14: Difference in the Rates of Safety Events**

Rate in Placebo VR Arm	Rate in a Drug Containing VR Arm Detectable with 90% Power
8.3%	69.3%
16.7%	79.0%
25.0%	87.0%
33.3%	93.4%
41.7%	99.2%

#### **10.4.2 Pharmacokinetic Endpoints**

Pharmacokinetic endpoints will include concentration-time course, maximum concentration ( $C_{max}$ ), and time to maximum concentration ( $T_{max}$ ), assessed in blood and tear test strips for each study drug. Day 28 concentration at time of ring removal will be described and drug half-life after ring removal will be estimated in blood, tear test strips, and cervical tissue. The sample size of the study is driven by the safety endpoints as described above.

#### **10.4.3 Acceptability Endpoints**

Several components of acceptability (e.g., ease of insertion and removal, genitourinary discomfort, awareness/feeling the study VR during daily activities, emotional comfort wearing the ring continuously for 28 days, willingness to use an HIV protective ring in the future, if one were available) will be used to assess overall acceptability. Each component will be assessed by a combination of dichotomous measures and rating scales where women will be categorized into (1) those reporting no acceptability issues during the 28 days of study VR use (e.g., those reporting no genitourinary discomfort) and (2) those reporting at least one issue during the 28 days of study VR use (e.g., those reporting some discomfort), and if yes, the intensity or severity of the issue (on a scale from 1 to 10). An acceptability endpoint is defined as a negative report by a participant, on any of the above components for acceptability. A sample size of 48 women will provide a precision of 13.0% (i.e., half the width of the 95% confidence interval) assuming an observed acceptability of 75%.

#### **10.4.4 Adherence Endpoints**

Adherence will be measured by the percentage of women who keep the VR inserted at all times in the vagina over the course of 28 days. A sample size of 48 women will provide a precision of 13.0% (i.e., half the width of the 95% confidence interval) assuming an observed adherence of 75%.

#### **10.5 Participant Accrual, Follow-up and Retention**

Based on previous studies of vaginal products with similar eligibility requirements, the accrual of 48 eligible participants will take approximately 6 months. Women lost to follow-up and/or on temporary hold or permanent product discontinuation will not be replaced. However, every effort will be made to complete their regularly scheduled safety evaluations. Each site will target retention of 95% of enrolled participants over the 52 day follow-up period.

#### **10.6 Randomization**

Participants will be randomized in a 1:1:1:1 ratio to the four arms of the study. Study arm randomization will be stratified by site to ensure balanced assignment of products

at each site. Participants will also be randomized in a 1:1:1 ratio to the three, end of study period PK/PD sampling times. This randomization will be stratified by site to ensure balanced assignment of PK/PD end of study period sampling timing. Both randomization schemes will be generated and maintained by the MTN SDMC.

The SDMC will provide each study site with one set of randomization envelopes to be stored and used in the study clinic. A sufficient number of envelopes will be assigned to each site so that they may potentially enroll up to 24 participants. Clinic staff will assign these envelopes in sequential order, by envelope number, to eligible participants. Each randomization envelope will include study product arm randomization assignment as well as end of study period PK/PD sampling time assignment.

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 to which the participant was assigned. Clinic staff will store assigned randomization envelopes and their contents in participants' study charts.

## **10.7 Blinding**

Study staff and participants will be blinded to the treatment assignments of all study participants. All VRs will be individually packaged and labeled. Multiple codes will be utilized to conceal and protect randomization assignments and the identity of the content of the ring.

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.

There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. As described in Section 9, 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 study product 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.

## **10.8 Data and Safety Monitoring and Analysis**

### **10.8.1 Study Monitoring Committee**

No Data and Safety Monitoring Board oversight is planned for this study. The MTN SMC will conduct interim reviews 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. These reviews will take place approximately every 4-6 months, and as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

### **10.8.2 Primary Analysis**

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Within-treatment group assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). When use of formal testing to assess differences between users of the placebo VR and users of one of the drug containing VRs is required, the following methods will be used: for binomial response variables, chi-square tests and logistic regression (or exact testing methods); 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 each of the four 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.

#### Safety Endpoints

All visits in which a woman has been exposed to the study product will be included in the primary analyses of safety. Secondary intent to treat analyses may also be performed. To assess genitourinary safety, the number and the percentages of participants experiencing each safety endpoint (see section 10.2) will be tabulated by study arm. Each participant will contribute once in each category (i.e., only for highest severity AE for each participant) for the calculation of event rates. Exact binomial confidence intervals will be calculated for each safety endpoint for each arm and Fisher's Exact test used to test for differences in event rates between each drug containing VR arm and the placebo VR arm.

#### Pharmacokinetic Analysis

Blood and CVF will be analyzed for routine PK parameters -  $C_{max}$ ,  $T_{max}$ , and AUC - and described using descriptive statistics. Half-life will be estimated for both drugs in blood, CVF, and cervical biopsies during the period following ring removal. Measures of drug exposure (AUC,  $C_{max}$ ) will be compared between arms and concentration differences will be analyzed.

### **10.8.3 Secondary Analyses**

#### Acceptability

To assess acceptability of the study VR, the number and percentage of participants experiencing at least one negative report of acceptability, including genitourinary discomfort and ring insertion/removal issues will be presented. This binomial proportion will be used to assess the acceptability of the study VR along with its corresponding 95% confidence interval.

The above acceptability analysis will be supplemented by presenting the above proportion by randomization arm along with its corresponding 95% confidence interval.

#### Adherence

To assess adherence of women to the VR, the proportion of participants who kept the study VR inserted at all times during the 28 days will be calculated along with a 95% confidence interval. For women who were not fully adherent, the number of removal/expulsion events and average duration of these events will be reported. Additionally, the average cumulative period of time during the study period when the study VR was outside the vagina will be calculated. Number, type and circumstances of expulsions (voluntary and involuntary) will be described.

### **10.8.4 Missing Data**

We are targeting a retention rate of 95% over the 52 day study period. Based on previous HIV Prevention Trials Network (HPTN) and MTN trials, we expect to have minimal missing data. If missing data rates are higher than anticipated (over 10%), robust methods such as nonparametric tests and generalized estimating equations (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. Electronic study questionnaires (CASI questionnaires) will be developed by the protocol Behavioral Scientist in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents. CRF data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system. CASI questionnaire data are entered directly into and stored on a secure MTN SDMC-hosted web server.

## 11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with current DAIDS policies. (<http://rsc.tech-res.com/policiesandregulations/>)

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations regarding testing investigational products, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval for the study products being tested 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 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 current DAIDS policies. (<http://rsc.tech-res.com/policiesandregulations/>)

# 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 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 by authorized representatives of the MTN CORE, IPM, SDMC, NL, NIAID, FDA, OHRP, IRBs/ECs and other 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/designee will have obtained IRB approval and the protocol will have been submitted to the FDA. The IoR/designee will permit audits by the NIH, IPM, the FDA, OHRP, MTN CORE, IRBs/ECs, SDMC, and other local and US regulatory authorities or any of their appointed agents.

### **13.1 Institutional Review Boards**

Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent forms, and study-related documents (such as participant education and recruitment materials) are reviewed by an IRB 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.

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

### **13.2 Protocol Registration**

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local IRB 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 (PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.



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

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

#### General

Phlebotomy may lead to excessive bleeding, discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Pelvic examination may cause mild discomfort and/or vaginal bleeding or spotting. Disclosure of HIV and STI status may cause worry, sadness or depression. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial as well as social isolation. Trained counselors will be available to help participants deal with these feelings. Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions when discussing sexual behaviors.

Participants at 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 product.

Use of the study VR may lead to vaginal symptoms, including irritation, increased discharge, and discomfort (including with vaginal intercourse).

Cervical biopsies carry the risk of discomfort or pain during the procedure and for a few hours afterwards. Participants may have mild vaginal spotting (bleeding) for one or two days, and will be instructed to avoid sexual intercourse and product use for the duration of the study. While abstinence is a requirement of this study, if participants are sexually active they may also be at increased risk for STIs and HIV acquisition, if exposed. Also some temporary discomfort with sexual intercourse may occur if the biopsy areas are still healing. There is a small risk of infection and heavier bleeding. Participants will be instructed to contact the clinic if symptoms are bothersome, if heavy bleeding is noted (soaking through a pad in an hour or less) or if the participant develops any abnormal odor or discharge from the vagina.

Based on adverse events reported among female participants in previous studies, Dapivirine VRs may be associated with:

- Vaginal bleeding
- Headache
- Fatigue
- Vulvovaginal or genital itching
- Abdominal discomfort
- Abdominal pain
- Urinary incontinence
- Nausea
- Vaginal or genital discharge

The following serious side effects have been associated with the use of oral maraviroc. These side effects may or may not be associated with maraviroc when formulated in a vaginal ring.

- Liver problems (liver toxicity) have occurred in people who took maraviroc. An allergic reaction may happen before liver problems occur. People who are co-infected with hepatitis B or C might be at higher risk of having liver problems.
- Heart problems, including heart attack.
- Low blood pressure when standing up, which can cause dizziness or fainting. People who have serious kidney problems may be at increased risk.

In addition to the serious side effects listed above, additional side effects include:

- Colds
- Cough
- Fever
- Rash
- Dizziness
- Diarrhea
- Swelling of parts of the body
- Flu and flu-like symptoms
- Muscle aches, spasms and pain
- Stomach pain and bloating
- Sleeping problems
- Runny, congested nose
- Problems with urination
- Low white blood cell counts (neutropenia)

Note: With oral maraviroc, there is a possible increased risk for getting other infections or cancer, although there is no evidence from the clinical trials of an increase in serious infections or cancer.

### **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, pelvic examination, and routine laboratory testing related to blood, liver, and kidney function. Participants may be provided or referred for STI treatment in accordance with CDC guidelines. 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 long-term 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 Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (<http://rsc.tech-res.com/policiesandregulations/>). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

In addition to informed consent forms, the Protocol Team will work with study staff and community representatives to develop 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 need to abstain from sexual intercourse, regardless of study treatment group
- The importance of participants in all four study groups to the success of the study
- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The real yet limited benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

### **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:

- Representatives of the US Federal Government, including the US FDA, the US OHRP, NIH, and/or contractors of the NIH, and other local and US regulatory authorities
- Representatives of IPM
- Study staff
- Site IRBs/ECs

The MTN has applied for a Certificate of Confidentiality from the US Department of Health and Human Services that is 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 Pregnant Women**

Women who test positive for pregnancy at Screening or Enrollment Visits will not be eligible to participate in this study. Should a woman test positive for pregnancy after Enrollment, a product discontinuation will be implemented but all follow-up visits will be completed and data collected per Section 7.5.2. During the informed consent process, women will be informed that the study VR is not a method of contraception and the effects of the study VR on a developing human fetus are unknown.

All potential participants are required by the Eligibility Criteria for Screening and Enrollment to be currently sexually abstinent for the duration of study participation. Women who become pregnant during the study period following randomization and exposure to study product will discontinue product use but not be excluded from analysis.

### **13.7.2 Children**

The NIH has mandated that children be included in research trials when appropriate. This study meets “Justifications for Exclusion” criteria for younger children as set forth by the NIH. Specifically, “insufficient data are available in adults to judge potential risk in children” and “children should not be the initial group to be involved in research studies.” This study does not plan to enroll children under 18 years old.

### **13.8 Compensation**

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

### **13.9 Communicable Disease Reporting**

Study staff will comply with local requirements to report communicable diseases including HIV-1 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-1 screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV-1 testing time point. Testing will be performed in accordance with the algorithm in Appendix II. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will emphasize the unknown efficacy of the study products in preventing HIV-1 infection. In accordance with the policies of the NIH, participants must receive their HIV-1 test results to take part in this study.

#### **13.10.2 Care for Participants Identified as HIV-Positive**

##### Identified as HIV-Positive Prior to Enrollment

An individual who has been identified as infected with HIV-1 will be referred for management according to the local standard of care.

##### Identified as HIV-Positive While on Study Product

Please refer to Section 9.6 for further details. Should a participant test positive for HIV after Enrollment follow-up procedures will be performed as per Section 7.5.1.

### **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, NIAID, NIMH, and IPM for review prior to submission.

## **15 APPENDICES**

## APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

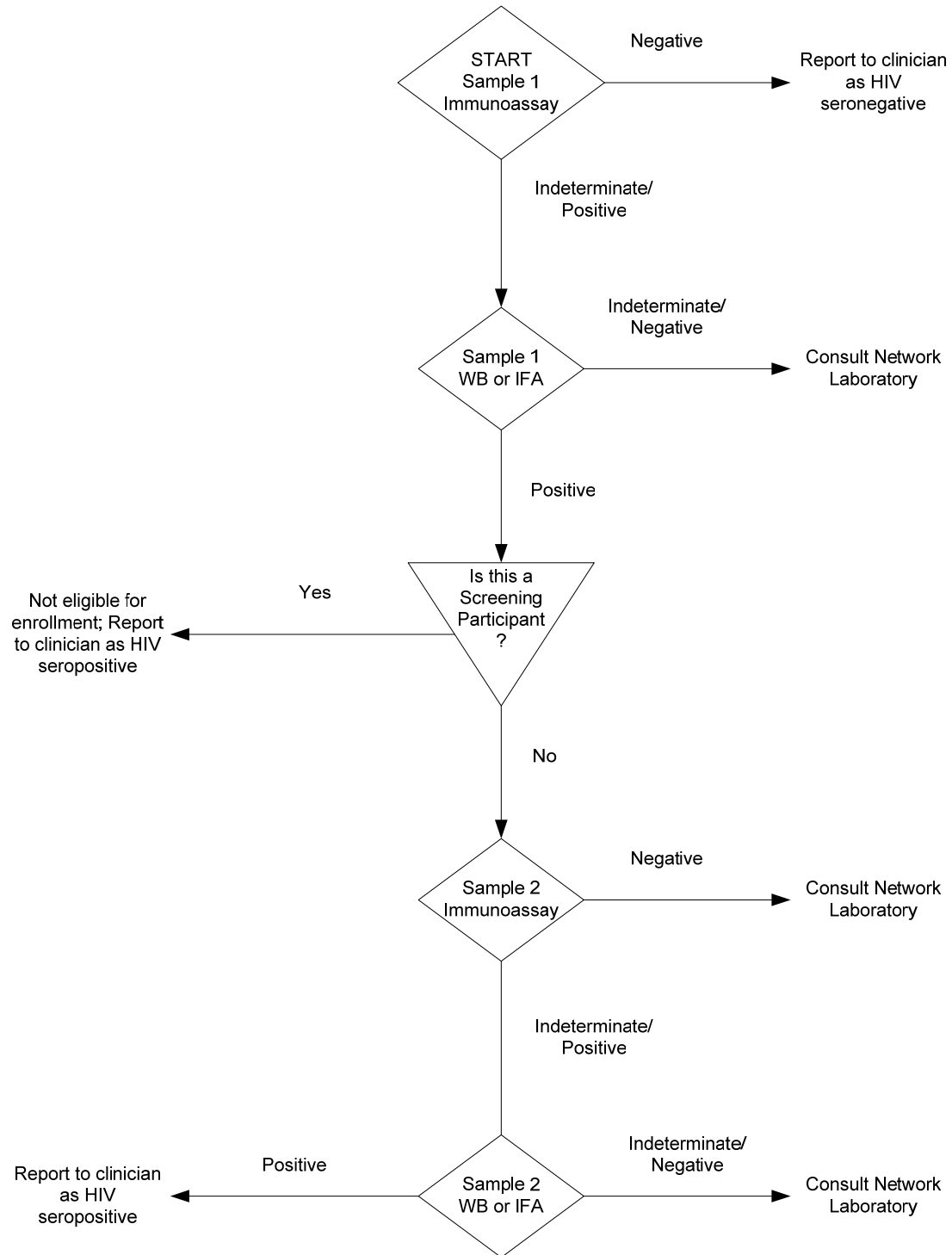
	SCR	ENR Day 0	VISIT DAYS 1, 2, 3, 5, 7, 14, 21	VISIT DAY 28	VISIT DAYS 29, 30	VISIT DAYS 31, 35, 42	DAY 52 Final Clinic/ Term.	Interim	
<b>ADMINISTRATIVE AND REGULATORY</b>									
Informed consent(s)	X	X							
Assess informed consent comprehension		X							
Assignment of PTID	X								
Locator information	X	X	X	X	X	X	X	*	
Demographic information	X								
Eligibility assessment	X								
Eligibility confirmation		X							
Randomization		X							
Reimbursement	X	X	X	X	X	X	X	*	
Schedule next visit	*	*	X	X	X	X	*	*	
Record/ update AEs			X	X	X	X	X	X	
<b>BEHAVIORAL</b>									
Conduct adherence assessment			☀	X			▲		
Conduct behavioral assessment	X	X		X			X		
Face-to-face interview				X					
HIV pre- and post- test counseling	X	X		*		*	X	*	
Contraceptive counseling	X	X	X	X	X	X	X	*	
HIV/STI risk reduction counseling	X	X	X	X	X	X	X	*	
Protocol adherence counseling		X	X	X	X	X		*	
Product use/adherence		X	X					*	
<b>CLINICAL</b>									
Medical and menstrual history	X	X	X	X	X	X	X	*	
Concomitant medications	X	X	X	X	X	X	X	*	
Document pre-existing conditions		X							
Physical examination	X	X	X	X	X	X	X	*	
Pelvic examination	X	X	X	X	*	±	X	*	
Provide available test results	X	X	X	X	X	X	X	X	
Treat or prescribe treatment for UTI/RTI/STIs or refer	*	*	*	*	*	*	*	*	
<b>LABORATORY</b>									
Urine	Collect Urine	X	X	*	X	*	±*	X	*
	hCG	X	X	☐*	X	*	±*	X	*
	Dipstick UA	X	*	*	*	*	*		*
	Urine culture	*	*	*	*	*	*		*
Blood	Collect Blood	X	X	X	X	X	X	X	*
	CBC with differential and platelets	X	X		X			X	*
	HIV-1 serology	X	X		*		*	X	*
	Chemistries	X	X		X			X	*
	PK- Blood		X	X	X	X	X	X	
	Syphilis serology	X							*
	Plasma archive		X						
Vaginal	Collect pelvic specimens	X	X	X	X	*	☐±*	X	*
	Vaginal fluid pH	*	X	◆*	X	*	☐	X	*
	Rapid Trichomonas test	X	*	*	*	*	*	*	*
	KOH wet mount for candidiasis	*	*	*	*	*	*	*	*
	Saline wet mount for BV	*	*	*	*	*	*	*	*
	NAAT for GC/CT	X	*	*	*	*	*	*	*
	PK- CVF (Tear test strips)		X	X	X		±	X	
	Vaginal swab for vaginal biomarkers (PD testing to be performed at Enrollment, Day 28, and Day 31)		X	◆	X		☐	X	
	Quantitative vaginal culture		X	◇	X			X	
	Gram stain		X	◆	X		☐	X	



Cervic at	Pap smear interpretation	*						
	Cervical tissue biopsy for PK				X		‡	
	Cervical tissue biopsy for PD				X			
<b>STUDY PRODUCT</b>								
	Provision of study product		X					
	Collect used study VR				X		▲	*
	Provide condoms						*	

X required; \*if indicated; ◆ on Day 3 only; ☼ Day 7, Day 14 and Day 21 visits only; ◇ Day 7 only; ▣ Required at Day 14; ‡ to be completed on randomization Day 31, Day 35, or 42 only; ■ Day 31 only; ▲ if early termination visit and not previously collected

## APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING



## APPENDIX III: SAMPLE INFORMED CONSENT DOCUMENT (SCREENING)

### SAMPLE INFORMED CONSENT FORM DIVISION OF AIDS, NIAID, NIH

MTN-013/IPM 026

#### Phase 1 Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring

Version 1.0

April 1, 2011

**PRINCIPAL INVESTIGATOR:** *[Sites to insert]*

**PHONE:** *[Sites to insert]*

**Short Title for the Study:** Safety and PK of a Dapivirine/Maraviroc VR

#### INFORMED CONSENT

You are being asked to volunteer for screening tests to find out if you are eligible for a research study known as MTN-013/IPM 026. This study is for women between the ages of 18 and 40 years old. Approximately 48 women will participate in this study across multiple sites. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). The products being used in this study [dapivirine vaginal ring (VR), maraviroc VR, maraviroc/dapivirine VR, placebo VR] are supplied by the International Partnership for Microbicides (IPM). The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to join this study, we want you to know about the study.

This is a screening consent form with information about the screening exams and tests. The screening exams and tests include interview questions, urine, and blood tests, a physical exam and an exam of your vagina. The study staff will explain the exams and tests to you and what is expected of you.

Your participation in this research is your decision. You may decide to withdraw from the study at any time without losing the benefits of your regular medical care.

#### YOUR PARTICIPATION IS VOLUNTARY

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

- Your participation is voluntary; you do not have to have the screening tests if you do not want to.

- You may decide not to have the screening tests, or to withdraw from the screening tests at any time, without losing your regular medical care.
- If you decide not to have the screening tests, you can still join another research study later, if one is available and you qualify. However, you cannot join the MTN-013/IPM 026 study if you are currently or have recently taken part in another study of drugs, medical devices or vaginal products.
- You are asked to tell the study staff about any other studies you are taking part in, or thinking of taking part in. This is very important for your safety.
- You are only being asked to have the screening tests at this time. Even if you agree to have the screening tests, you do not have to join this study.
- Some people may not be able to join this study because of information found during the screening tests.
- You will receive the results of the screening tests even if you are not eligible to join this study.
- If new information is learned about the study, or the study products, you will be told about this as soon as possible.

### **PURPOSE OF THE STUDY**

The main purpose of these screening exams and tests is to find out if you can join this research study. This research study will try to find out if dapivirine, maraviroc, and dapivirine/maraviroc VRs are safe and if there are any bad effects when women place a ring in the vagina for approximately 28 days. A vaginal ring is a flexible ring that may or may not contain a drug and is placed in the vagina. Another purpose of this study is to see if the study drugs (dapivirine and maraviroc) go into the bloodstream and into the vagina.

### **STUDY PRODUCTS**

All of the study products have been previously tested and one of the study drugs (maraviroc) is approved by the US Food and Drug Administration (FDA) for the treatment of Human Immunodeficiency Virus (HIV) in the pill form. HIV is the virus that causes AIDS. Drugs being tested by researchers to prevent HIV infection work in different ways.

Maraviroc works by interfering with the binding, fusion and entry of HIV into a human cell. Blocking this step slows the progression from HIV infection to AIDS in people found to be HIV-positive.

Dapivirine works by preventing HIV from making copies of itself, thereby stopping the replication of HIV. This study is not testing to see if the study drugs prevent HIV infection. Researchers do not yet know if these drugs when used in combination will work in humans to protect against HIV. The only known way to protect against getting HIV infection during sex is to use a condom every time you have sex.

While all of these study drugs have been tested before in humans, this is the first time maraviroc has been tested in a ring formulation in humans. This is also the first time

dapivirine and maraviroc have been tested in combination, in a VR form, in humans. Many studies have been conducted involving dapivirine VRs.

## **STUDY GROUPS**

If you decide to enroll in MTN-013/IPM 026, which will occur during a separate visit, and if you meet all of the study requirements, you will be randomized to one of four VR study groups; dapivirine VR, maraviroc VR, a combination VR containing dapivirine and maraviroc, and, finally, a placebo VR. A placebo vaginal ring is a ring that will look like the other rings but has no study drug or any other active ingredient in it. Twelve women will be in each study group and women will be assigned to a group by random chance (the equivalent of throwing dice). Women will be asked to place a ring in their vagina for approximately 28 days.

All of the study groups, including the groups with active product in the vaginal rings and the placebo vaginal ring group, are important to this study. No matter which study group you are in, you must remember that we do not know if the active study product rings work to protect women from getting HIV.

## **WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN THE SCREENING EXAMS AND TESTS?**

If you agree to have screening tests, they may be done today. If all tests are not completed today and you still want to find out if you can be in the MTN-013/IPM 026 study, you may come back another day. If you have to come back, some procedures may be repeated. MTN-013/IPM 026 has 16 study visits that will take place [sites to specify where visits will take place], including the Screening Visit which is taking place today.

### **Screening Visit:**

Your first visit will happen 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. The procedures done at this visit will take about [sites to insert time].

- Study staff will ask you where you live and other questions about you, your medical health (including what medications you are taking), menstrual history, your sexual practices and your understanding of the study requirements.
- Study staff will:
  - Perform a physical exam
  - Talk with you about the requirements of the study including, but not limited to:
    - Not having sex for the duration of your study participation
    - Contraception or being on an effective method of contraception, including hormonal methods, i.e., ‘the pill’, being sexually abstinent for longer than 90 days, sterile, etc.
    - Not using tampons for the duration of your study participation.
  - Test your urine for:
    - Pregnancy

- If you are pregnant you cannot join this study. If the study is still open after your pregnancy, you can come back here to find out if you are eligible then.
  - If you are not pregnant, you will talk with study staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex.
- Take a blood sample [Sites to insert amount]:
  - To test the health of your blood, liver and kidneys
  - To test for infections passed through sex, including HIV
    - You will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we know your status for sure. You must receive your HIV test results to be in the study. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need. Your partner(s) may also have access to free HIV counseling and testing, if needed. The study staff will tell you about other studies you may be eligible for, if any.
- Perform a pelvic examination:
  - The study doctor or nurse will use a speculum, a plastic or metal instrument used to separate the walls of the vagina. The study doctor or nurse will check your vagina and cervix for signs of infection, and other problems. They may also take some fluids to test for sexually transmitted infections or diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary.
  - The study staff may also collect samples from your cervix for a “Pap test” or “Pap smear” if you don’t have results from a Pap test done in the past 12 months. If the test is abnormal, it could mean you have cervical cancer, or that you should have more tests or treatment to lower your chances of having it turn into cervical cancer. It takes about [Sites to insert amount of time] before Pap test results are ready. If you have a written report confirming a normal Pap test in the past 12 months or if you had an abnormal Pap test but had follow-up indicating no treatment was required, you will not need to have a Pap test taken at this Screening visit. The results of your Pap test may affect whether or not you can continue in the study.
- Give you treatment or refer you for treatment for infections passed through sex, if needed.
- Give you referrals for other services if you or your partner(s) need them
- Provide you with the results of your tests, if available
- Schedule your next visit to enroll in MTN-013/IPM 026, if you are willing and eligible

- You also must agree to refrain for at least 5 days prior to your enrollment visit from inserting any non-study vaginal products or objects into the vagina; including any of the following, spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), douches, lubricants, sex toys (vibrators, dildos, etc.), and tampons

Results of tests listed above will be available within [*Sites to specify timeframe*] of your visit. If you decide not to join MTN-013/IPM 026, no blood collected at this visit will be kept or used for any tests other than those listed above. The study staff will review your test results with you when they are available. You may return when the results are available. If the results show you can join the MTN-013/IPM 026 study, the study staff will explain the study to you and answer any questions you have. If you decide to be in this study, you will be asked to sign another consent form.

## **RISKS AND/OR DISCOMFORTS**

**Risks of Blood Draws:** You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, small clot, or infection where the needle goes into your hand or arm.

**Risks of Pelvic Exams:** You may feel discomfort or pressure during the examination of your genital area and inside your vagina. You may have a small amount of vaginal bleeding which will stop shortly after the examination.

**Other Possible Risks:** You may become embarrassed and/or worried when discussing your sexual practices, ways to protect against HIV and other infections passed through sex, and your test results. You may become worried while waiting for your test results. If you have HIV or other infections, learning this could make you worried. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality while you are having the screening tests. Your visits will take place in private. However, it is possible others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your HIV status could also cause problems between you and your partner. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

## **BENEFITS**

You may receive no direct benefit from the screening tests. However, you will have a physical examination, pelvic examination, and tests to check on the health of your blood, liver, and kidneys. If these tests show that you might have health problems, you will be referred for medical care and other services available to you.

You will be counseled and tested for STIs. If you have these infections, you may be offered treatment for them, if needed. Also, if you would like to receive free male condoms at your final visit they will be provided to you. If you are infected with HIV, you will be referred for medical care, counseling, and other available services that could be of help to you. You can bring your sexual partner(s) here so we can also provide them with referral for diagnosis and treatment for possible STIs. For other health problems that cannot be treated at this clinic, the study staff will refer you to other places where you may receive medical care. If your Pap test result shows anything that is not normal, you will be referred for advice and/or treatment.

### **REASONS WHY YOU MAY BE WITHDRAWN FROM THE SCREENING TESTS WITHOUT YOUR CONSENT**

You may be withdrawn from the screening tests without your consent if:

- You are found to not be eligible for this study
- The study is stopped or canceled
- The study staff feel that having the screening tests would be harmful to you
- You are not willing to find out your HIV test result
- You are not able to attend clinic visits or complete the screening tests
- Other reasons are identified by study staff

### **COSTS TO YOU**

[*Site to complete according to site capacity*] There is no cost to you for screening tests. Treatments available to you from the study site for infections passed through sex will either be given to you free of charge or you will be referred for treatment while you are screening for this study.

### **REIMBURSEMENT**

[*Sites to insert information about local reimbursement:*] You will receive [*Sites to insert amount \$xx*] for your time, effort, and travel to and from the clinic at each scheduled screening visit.

### **CONFIDENTIALITY**

Efforts will be made to keep your personal information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff will use your personal information, if needed, to verify that you are not taking part in any other research studies. This includes studies conducted by other researchers that study staff knows about. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH
- IPM, the organization that supplies the study rings
- Study monitors



- Site Institutional Review Board (IRB)/ Ethics Committee (EC), an IRB is a committee that watches over the safety and rights of research participants
- Study staff

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

The researchers will do everything they can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have applied for a Certificate of Confidentiality from the US Federal Government. 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 give for study purposes. However, if the 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. This Certificate does not prevent you from releasing information about yourself and your participation in the study.

### **RESEARCH-RELATED INJURY**

*[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of having the screening tests. If you are injured, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you may receive additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.*

### **PROBLEMS OR QUESTIONS**

If you ever have any questions about the screening tests, 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/EC or other organization appropriate for the site] at [insert physical address and telephone number].*

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

**SIGNATURES**

*[Insert signature blocks as required by the local IRB/EC:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to have the screening tests, please sign your name below.

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Participant Name (print)	Participant Signature	Date
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Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
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## APPENDIX IV: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)

### SAMPLE INFORMED CONSENT FORM DIVISION OF AIDS, NIAID, NIH

MTN-013/IPM 026

#### Phase 1 Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring

Version 1.0

April 1, 2011

**PRINCIPAL INVESTIGATOR:** *[Sites to insert]*

**PHONE:** *[Sites to insert]*

**Short Title for the Study:** Safety and PK of a Dapivirine/Maraviroc VR

#### INFORMED CONSENT

You are being asked to take part in this research study because you are a woman between the ages of 18 and 40 years and have passed the screening for this study. Approximately 48 women will participate in this study across multiple sites. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). The products being used in this study [maraviroc vaginal ring (VR), dapivirine VR, maraviroc/dapivirine VR, placebo VR] are supplied by the International Partnership for Microbicides (IPM). The person in charge of this study at this site is *[INSERT NAME OF PRINCIPAL INVESTIGATOR]*. Before you decide if you want to join this study, we want you to know about the study. This Enrollment consent form gives you information about this study. The study staff will talk with you about it and answer your questions about this study. You may decide to withdraw from the study at any time.

#### YOUR PARTICIPATION IS VOLUNTARY

Once you read, discuss, and understand the study, and if you agree to take part, you will be asked to sign your name on this form. You will be offered a copy of this form to keep.

#### PURPOSE OF THE STUDY

This research study will try to find out if dapivirine, maraviroc, and dapivirine/maraviroc VRs are safe and if there are any bad effects when women place a ring in the vagina for approximately 28 days. A vaginal ring is a flexible ring that may or may not contain a drug and is placed in the vagina. Another purpose of this study is to see if the study drugs (dapivirine and maraviroc) go into the bloodstream and into the vagina.

## **STUDY PRODUCTS**

All of the study products have been previously tested and one of the study drugs (maraviroc) is approved by the US Food and Drug Administration (FDA) for the treatment of Human Immunodeficiency Virus (HIV) in the pill form. HIV is the virus that causes AIDS. Drugs being tested by researchers to prevent HIV infection work in different ways.

Maraviroc works by interfering with the binding, fusion and entry of HIV into a human cell. Blocking this step slows the progression from HIV infection to AIDS in people found to be HIV-positive.

Dapivirine works by preventing HIV from making copies of itself, thereby stopping the replication of HIV. This study is not testing to see if the study drugs prevent HIV infection. Researchers do not yet know if these drugs when used in combination will work in humans to protect against HIV. The only known way to protect against getting HIV infection during sex is to use a condom every time you have sex.

While all of these study drugs have been tested before in humans, this is the first time maraviroc has been tested in a ring formulation in humans. This is also the first time dapivirine and maraviroc have been tested in combination, in a VR form, in humans. Many studies have been conducted involving dapivirine VRs.

## **STUDY GROUPS**

All of the eligible women will be randomized to one of four VR study groups; dapivirine VR, maraviroc VR, a combination VR containing dapivirine and maraviroc, and, finally, a placebo VR. A placebo vaginal ring is a ring that will look like the other rings but has no study drug or any other active ingredient in it. Twelve women will be in each study group and women will be assigned to a group by random chance (the equivalent of throwing dice). Women will be asked to place a ring in their vagina for approximately 28 days.

All of the study groups, including the groups with active product in the vaginal rings and the placebo vaginal ring group, are important to this study. No matter which study group you are in, you must remember that we do not know if the active study product rings work to protect women from getting HIV.

## **WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN MTN-013/IPM 026?**

If you decide to enroll in the study, some procedures will occur today. After today you will be in the study for about 7½ weeks. You will have a visit here today (Day 0), and on Days 1, 2, 3, 5, 7, 14, 21, 28, 29, 30, 31, 35, 42, and 52 for a total of 15 visits. Procedures done at these visits will take approximately [site to insert].

### **At your first visit you will:**

- Be randomly assigned by study staff to one of four study groups. Neither you nor study staff will know which group you are in, choose your group or change the

group you have been placed into. Women in the study groups will have the same study visit schedule.

- Answer questions to confirm that you are able to join the study and that you understand what the requirements of this study are.
- Discuss any health or medical problems that you may have had for some period of time, these are often called preexisting conditions
- Provide a blood sample [insert amount] in case there is a question about your lab results in the future. After all testing is done, this sample will be destroyed according to the site's procedure for getting rid of blood samples that will not be needed after the study ends.
- Receive and insert the study ring. Study staff may assist you with ring insertion if you cannot do it on your own. All participants will have an exam to ensure that the ring is inserted correctly.

At all study visits you will:

- Provide study staff with information about where you live and how we can contact you or update study staff with this information
- Tell study staff about any changes in your health (including what medicines you are taking) and your menstrual periods.
- Tell study staff if you have had any health problems or other problems having to do with the study including the vaginal ring since your last visit, except at your Enrollment Visit
- Have a physical exam
- Talk with study staff about the following:
  - What the rules of the study are and how to follow the rules (except at your final visit)
  - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex
  - Contraception and ways to avoid getting pregnant (except at your final visit)
- Receive treatment or be referred for treatment for problems that the study staff may find.
- Have blood collected to see how much study product(s) get absorbed by your body. The amount of blood collected will not exceed [Sites to insert amount]
- Receive test results, if they are available
- Schedule your next visit (except at your Day 52 visit)

At other study visits you will:

- Provide a sample of blood to:
  - Check the health of your blood, liver and kidneys at the Enrollment Visit and on Days 28 and 52
  - Test for HIV at your Enrollment Visit and on Day 52:
    - You will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results and how you feel about them, and ways to prevent HIV and other STIs. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that

case, we will do more tests until we know your status for sure. You must receive your HIV test results to be in the study. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need. Your partner(s) may also have access to free HIV counseling and testing if needed. The study staff will tell you about other studies you may be eligible for, if any.

- Provide a urine sample to see if you are pregnant at the Enrollment Visit and on Day 14, Day 28, Day 31, 35, or 42, and Day 52
- Have a pelvic examination at Enrollment, Day 1, Day 2, Day 3, Day 5, Day 7, Day 14, Day 21, Day 28, Day 31, 35 or 42, and at your final clinic or early termination visit.
  - The study doctor or nurse will use a speculum. Study staff will ask if you are experiencing symptoms of an infection. They will check your vagina and cervix for signs of problems due to the ring or infection. They will also take some fluids to test for bacteria and organisms in the vagina and, if necessary, look for any other problems.
  - At Enrollment, Day 3, Day 7, Day 28, Day 31, 35 or 42 and at your final clinic visit or early termination visit you will have samples collected to test for any changes in your vaginal fluid that might have occurred due to the use of the vaginal ring
- Talk with study staff about how to properly wear and use the study ring at your Enrollment Visit, Day 1, Day 2, Day 3, Day 5, Day 7, Day 14, and Day 21.
- You or the study clinician, will remove the vaginal ring in the clinic at the Day 28 visit. Study researchers may keep this ring to run additional tests on it.
- Answer questions about your experience using the vaginal ring, including whether or not the ring was removed from or fell out of your vagina (Enrollment Visit and Day 7, Day 14, Day 21, Day 28). You may use a computer to answer these questions or a staff member may ask you these questions. You will also be interviewed by study staff at your clinic visit on Day 28 to talk about your experience.
- You will also have the following procedures performed to see how much study products are absorbed by your body:
  - Provide vaginal and cervical fluid by tear test strips at the following visits: Enrollment, Day 1, Day 2, Day 3, Day 5, Day 7, Day 14, Day 21, Day 28, Day 31, 35 or 42 and Day 52. A tear test strip is a special piece of paper that gets inserted into your vagina to collect cervical and vaginal fluid.
  - You will be asked to give tissue samples (biopsies) from your cervix at the Day 28 visit and on one of the following visits, either Day 31, 35, or 42. A study clinician will collect this biopsy using a special medical tool specifically designed to collect these samples. Approximately 2 to 3 samples will be collected, each about 3 mm by 5 mm around, or as big as a grain of rice.
  - Provide blood samples on Day 1, Day 2, Day 3, Day 5, Day 7, Day 14, Day 21, Day 28, Day 29, Day 30, Day 31, 35 or 42 and Day 52. At the enrollment and day 28 visits, we will ask you to stay at the clinic for blood draws at five time points (hr 0, 1, 2, 4, and 6).

- Also, you will be asked questions about vaginal practices that may effect how the study drug is absorbed by your body on any of the days that samples are collected
- Receive male condoms at your final visit, if you need them

At any time during the study, the following may need to be collected if you are having symptoms or if clinicians suspect you may have an infection:

- Have vaginal and/or cervical swabs collected to test for infections
- Have a blood sample [Sites to insert amount] collected to test:
  - For infections passed through sex
  - For HIV
  - The health of your blood, liver and kidneys
- Have urine collected to test for:
  - Pregnancy
  - Infection

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.

### **If you become infected with HIV**

As a requirement of this study you are asked to **NOT** engage in any sexual activity. Your participation in this study will not cause HIV infection. However, there is always a chance that through sexual activity or other activities you may become HIV-positive. In the unlikely event that you become HIV-positive, study staff will give you counseling and refer you for medical care and other available services. You will continue to be counseled while you are in this study. You will have more tests to find out how well some HIV drugs might work for your type of HIV (HIV drug resistance). If the HIV tests confirm that you have been infected with HIV, you will stop using the ring, but we will ask that you continue to come into the office for regularly scheduled visits for some of the study procedures. You may be referred to other research studies.

### **RISKS AND/OR DISCOMFORTS**

Whenever your blood is drawn, you may:

- Have excessive bleeding
- Discomfort
- Feelings of dizziness or faintness
- Bruising, swelling and/or infection

During or after genital exams, you may feel discomfort or pressure in your genital area and inside your vagina. You may also have slight vaginal bleeding which will stop shortly after the examination.

During pelvic exams and the tear test strip collection, you may feel discomfort or pressure in your vagina and/or pelvis. From the pelvic exam you may also have vaginal bleeding or spotting.

You may feel slight to moderate pain at the time of the biopsy (like being pinched) which usually resolves quickly, but could last a few hours. You may have spotting (small amounts of vaginal bleeding) for 1 – 2 days. You are required to be abstinent during this study; people who are sexually active immediately following a biopsy collection may be at increased risk for STIs and HIV acquisition, if exposed. There is a small risk of the biopsy area becoming infected or having bleeding that is heavier than spotting. It is important for you to know your body is healing for 24-48 hours after the biopsy is collected. However, if you have bleeding heavier than your usual menstrual period, a foul odor or a heavier vaginal discharge (more than usual), you should contact the study clinic right away.

### **Risks of Study Rings**

The study rings can cause some side effects. We do not yet know all the side effects of the rings. Some, but not all women who used the rings in other studies have had:

- Discharge from the vagina
- Irritation and discomfort

### **Risks of Study Drugs**

Based on side effects reported among women in previous studies, Dapivirine VRs may be associated with:

- Vaginal bleeding
- Headache
- Fatigue
- Vulvovaginal or genital itching
- Abdominal discomfort
- Abdominal pain
- Urinary incontinence
- Nausea
- Vaginal or genital discharge

The following serious side effects have been associated with the use of oral maraviroc:

- Liver problems (liver toxicity) have occurred in people who took maraviroc. An allergic reaction may happen before liver problems occur. People who are co-infected with hepatitis B or C might be at higher risk of having liver problems
- Heart problems, including heart attack
- Low blood pressure when standing up, which can cause dizziness or fainting. People who have serious kidney problems may be at increased risk



In addition to the side effects listed above, additional side effects include:

- Colds, cough, fever, rash, dizziness, diarrhea, swelling of parts of the body, flu and flu-like symptoms, muscle aches, spasms and pain, stomach pain and bloating, sleeping problems, runny/congested nose, problems with urination, low amounts of white blood cell counts (neutropenia)

Note: There is a possible increased risk for getting other infections or cancer, although there is no evidence from the clinical trials of an increase in serious infections or cancer.

The risks associated with Maraviroc VRs and Dapivirine/Maraviroc VRs are not known.

### **Other Possible Risks**

You may become embarrassed and/or worried when discussing your sexual practices, ways to protect against HIV and other infections passed through sex, and your test results. You may be worried while waiting for your test results. If you have HIV or other infections, learning this could make you worried. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your HIV status could also cause problems between you and your partner. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

### **Pregnancy, Breastfeeding and Sexual Practices**

The rings with active drug and the placebo ring are not birth control methods. You must agree to use an effective method of birth control such as birth control pills or another hormonal-based method (except for vaginal rings), or an intrauterine device (IUD), unless you are sterilized, identify as a woman who has sex with women exclusively; and/or have been sexually abstinent for more than 90 days. You must also agree to not insert anything into your vagina for the duration of this study; this means that you may not have sex for the duration of this study. Sex for this study is defined as receptive penile intercourse, anal intercourse, receptive oral intercourse and the use of sex toys. You must also agree to not use tampons while on your period and for the duration of your study participation.

We do not know what effect the study drugs have on pregnancy, including the effect of the study drug on the fetuses of women who use the vaginal ring when pregnant, or the babies of women who use the vaginal ring when breastfeeding. Because of

this, pregnant women and women who are breastfeeding may not join this study. Women who join the study must agree to avoid sexual intercourse, use an effective contraception and have scheduled pregnancy tests while in the study.

**If you do not think you can be sexually abstinent for 52 days then you should not enroll in this study.**

If you become pregnant during the study, study staff will refer you to available medical care and other services you or your baby may need. The study does not pay for this care. You will stop using the ring, but we will ask you to keep coming here for study visits as originally planned. We will change the study procedures as needed to protect your health while you are pregnant. *[Sites to include/amend the following: We may also contact you to find out about the health of your pregnancy, and the health of your baby up to one year old, if you have a baby. We may also contact you about a study that collects information about pregnancy and babies up to one year old.]* The outcome of your pregnancy is important to study staff; therefore your pregnancy will be followed until the results of your pregnancy are known.

**BENEFITS**

No one knows if the study ring will prevent HIV infection. Information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive pelvic exams and counseling and testing for HIV and STIs. You will also have tests to check the overall health of your liver, kidneys, and blood cells.

This study cannot provide you with general medical care, but study staff will refer you to other available sources of care.

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

**NEW INFORMATION**

You will be told any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the ring may be causing bad effects, you will be told about this. You will also be told when study results may be available, and how to learn about them.

## **WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT**

A study doctor may need to remove you from the study early without your permission if:

- The study is cancelled by the US FDA, US NIH, the International Partnership for Microbicides, the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/ the Ethics Committee (EC). An IRB is a committee that watches over the safety and rights of research participants
- The Study Monitoring Committee (SMC) recommends that the study be stopped early (A SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study)
- You are not able to keep appointments
- Other reasons that may prevent you from completing the study successfully

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

- You become pregnant or you are breastfeeding
- You become infected with HIV
- A study doctor decides that using the vaginal ring would be harmful to you
- You require a treatment that you may not take while using the study vaginal ring
- You have a bad reaction to the study vaginal ring

If a study doctor asks you to stop using the ring, you will need to come in for all scheduled visits described above, including the physical examination, vital signs, and blood tests. You will stop using study ring until the study doctor decides it is safe for you to start using it again, if possible.

In the event that you are removed from or choose to leave this study, you will be asked to return your vaginal ring. If you do not have the vaginal ring with you at the time of your contact with staff, staff members will make every effort to assist you in returning the ring as soon as possible. *[Sites to specify allowances for special circumstances.]*

## **COSTS TO YOU**

*[Site to complete according to site capacity]* There is no cost to you for study related visits, the vaginal ring, physical examinations, laboratory tests or other procedures. Treatments available to you from the study site for infections passed through sex will be given to you free of charge or you will be referred for available treatment for the duration of the study.

## **REIMBURSEMENT**

*[Sites to insert information about local reimbursement:]* You will receive *[Sites to insert amount \$xx]* for your time, effort, and travel to and from the clinic at each

scheduled visit. You may receive [Sites to insert amount \$xx] for any visits which occur in between your normally scheduled visits.

## **CONFIDENTIALITY**

Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff may use your personal information to verify that you are not in any other research studies. This includes studies conducted by other researchers that study staff know about. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US Food and US FDA, US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH
- IPM, the organization that supplies the study vaginal rings
- Study monitors
- Site IRB/EC
- Study staff

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

The researchers will do everything they can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have applied for a Certificate of Confidentiality from the US Federal Government. 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 give for study purposes. However, if the 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. This Certificate does not prevent you from releasing information about yourself and your participation in the study.

## **RESEARCH-RELATED INJURY**

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

## **YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER**

*[Sites to specify institutional policy:]* Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic. If you want the results of the study after the study is over, let the study staff members know.

## **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/EC or other organization appropriate for the site]* at *[insert physical address and telephone number]*.

**SIGNATURES**

*[Insert signature blocks as required by the local IRB/EC:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to have the study, please sign your name below.

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Participant Name (print)	Participant Signature	Date
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Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
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**APPENDIX V: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)**

**SAMPLE INFORMED CONSENT FORM  
DIVISION OF AIDS, NIAID, NIH**

**MTN-013/IPM 026**

**Version 1.0**

**April 1, 2011**

**PRINCIPAL INVESTIGATOR:** *[Sites to insert]*

**PHONE:** *[Sites to insert]*

**Short Title for the Study:**

**INTRODUCTION**

You have decided to join the MTN-013/IPM 026 study funded by the United States National Institutes of Health. While you are in this study, there may be some blood, vaginal/cervical fluids and/or cervical tissue taken from you that might be useful for future research. You are being asked to agree to the storage of these samples. This consent form gives you information about the collection, storage, and use of these samples. The study staff will talk with you about this information. Please ask study staff any questions you may have. You will be asked to sign this form to indicate whether you agree to have your blood, vaginal/cervical fluid and/or tissue stored and tested in the future. You will be offered a copy of this form to keep.

**HOW WILL YOU GET THE SAMPLES FROM ME?**

You have agreed to have your blood, vaginal/cervical fluid and cervical tissue tested as part of the MTN-013/IPM 026 study. During the study, your stored blood and vaginal/cervical fluid will be tested to check your health and to see if you have HIV or other infections passed by having sex. The study staff would like to save any extra blood, vaginal/cervical fluid and/or tissue samples that are leftover, after the study is done, to use for future testing. If you agree to this, no additional blood, cervical/vaginal fluid and/or tissue will be taken from you. Only leftover samples will be kept and used for future testing.

**HOW WILL YOU USE MY SAMPLES?**

Your samples will only be used to look for ways that your body responds to infection. For instance, researchers may look at your blood cells and substances in your blood, vaginal/cervical fluid and/or tissue called proteins and chemicals. They also may look at your genes (material passed from parent to child that determines the make-up of the body and mind), since your genes might affect how your body responds to disease. Your genes might make you more likely or less likely to get an infection, or affect your responses to infection or to treatment. No other kinds of genetic tests will be done by anyone on your stored samples without first explaining

the test to you and obtaining your permission. The researchers do not plan to contact you or your regular doctor with any results from tests done on these leftover samples. This is because research tests are often done in ways that are experimental, so the results do not usually help doctors manage your health. If a rare situation comes up in which the researchers decide that a test result is important for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your contact information. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name and contact information.

Your samples will not be sold or used directly to produce commercial products. Research studies wishing to use your samples will be reviewed by the National Institutes of Health and a special committee at the researcher's institution (an Institutional Review Board). The role of this committee is to protect you and other research volunteers from harm.

#### **HOW WILL MY SAMPLES BE STORED AND FOR HOW LONG?**

Your extra blood, vaginal/cervical fluid and/or tissue will be stored at facilities in the United States that are designed to store samples safely and securely. The facilities are designed so that only approved researchers will have access to the samples. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. There is no time limit on how long your samples will be stored.

#### **DOES STORAGE OF MY SAMPLES BENEFIT ME?**

There are no direct benefits to you, however information learned from this study may help others.

#### **WHAT ARE THE RISKS?**

There are few risks related to storing your samples. When tests are done on the stored samples, there is a small but possible risk to your privacy. If others found out about test results (such as information about your genes), it could cause you problems with your family, (such as having a family member learn about a disease that may be passed on in families) or problems getting a job or insurance.

#### **WHAT ABOUT CONFIDENTIALITY?**

To keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your name and other personal information 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. Any publication about the results of future tests will not use your name or identify you



personally. The researchers will do everything they can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have applied for a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with the research, such as the court system, about your participation. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Individuals that may review your records include:

- Representatives of the US Federal Government, including the US Food and US FDA, the US Office for Human Research Protections (OHRP), NIH, and/or contractors of the NIH
- International Partnership for Microbicides (IPM), the organization that supplies the study vaginal rings
- Study monitors and their designees
- Site Institutional Review Board (IRB)/Ethics Committee (EC)
- Study staff

### **WHAT ARE MY RIGHTS?**

Allowing your samples to be stored is voluntary. If you decide not to have any samples stored other than what is needed to complete the MTN-013/IPM 026 study, you can still stay in the study, and your leftover samples will be destroyed. If you decide now that your samples can be stored for future research, you may change your mind any time. However, you must contact your study doctor or nurse and let them know that you no longer want your samples used for future research. Your samples will then not be used and will be destroyed.

### **WHAT DO I DO IF I HAVE QUESTIONS?**

If you have questions about the storage and future testing of your leftover specimens, contact *[insert the name of the investigator]* at *[insert physical address and telephone number]*.

If you have questions about your rights related to the storage and future testing of your samples for research, contact *[insert the name or title of person on the Institutional Review Board]* at *[insert physical address and telephone number]*.

**SIGNATURES**

Please carefully read the statements below and think about your choice. No matter what you decide, it will not affect your participation in the MTN-013/IPM 026 study or your medical care. Please sign below and initial whether or not you agree to allow leftover sample(s) to be stored for future testing.

*[Insert signature blocks as required by the local IRB/EC, yes/no boxes may be used for each specimen type:]*

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Participant Name (print)	Participant Signature	Date
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Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
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I agree to allow the following leftover samples to be stored and used for future testing (please initial)

\_\_\_\_\_ Blood

\_\_\_\_\_ Vaginal and/or cervical fluid

\_\_\_\_\_ Cervical tissue

OR

\_\_\_\_\_ I do not agree to allow any of my leftover blood, vaginal/cervical fluid and/or cervical tissue to be stored and used for future testing

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