

**MTN-029/IPM 039**

**Phase 1 Pharmacokinetic Study of the Dapivirine Vaginal Ring in Lactating Women**

**Microbicide Trials Network**

**Funding Agencies:**

**Division of AIDS, US National Institute of Allergy and Infectious Diseases  
US *Eunice Kennedy Shriver* National Institute of  
Child Health and Human Development  
US National Institute of Mental Health  
US National Institutes of Health**

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**IND #108,743**

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**Version 1.0**

**June 30, 2015**

**MTN-029/ IPM 039**

**Phase 1 Pharmacokinetic Study of the Dapivirine Vaginal Ring in Lactating Women**

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### Phase 1 Pharmacokinetic Study of the Dapivirine Vaginal Ring in Lactating Women

#### LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ARV	antiretroviral
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
AST	aspartate aminotransferase
b.i.d.	bis in die (twice a day)
BV	bacterial vaginosis
CAB	community advisory board
CDC	U.S. Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
C <sub>max</sub>	maximum concentration
CMRB	Clinical Microbicide Research Branch
CRF	Case Report Form
CROI	Conference on Retroviruses and Opportunistic Infections
CRS	Clinical Research Site
CT	Chlamydia trachomatis
CTA	clinical trial agreement
CVF	cervicovaginal fluid
CWG	Community Working Group
DAERS	DAIDS Adverse Events Reporting System
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAPY	di-aminopyrimidine
DLV	delavirdine
DNA	deoxyribonucleic acid
DPV	dapivirine
DSMB	Data and Safety Monitoring Board
EAE	expedited adverse event
EC	effective concentration
EC	Executive Committee
EFV	efavirenz
FDA	Food & Drug Administration (U.S.)
FHCRC	Fred Hutchinson Cancer Research Center
GC	Neisseria gonorrhoeae
GCP	Good Clinical Practice
GMP	good manufacturing practices
HEENT	head, eye, ear, nose and throat examination
HHS	U.S. Department of Health and Human Services
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus – Type 1
hu-SCID	humanized severe combined immunodeficient
IATA	International Association of Air Transport
IB	Investigator's Brochure
ICF	Informed Consent Form
IND	Investigational New Drug
IoR	Investigator of Record

IP	investigational product
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
IUD	intrauterine device
LDMS	Laboratory Data Management System
LC	Laboratory Center
LOC	Leadership and Coordinating Center
mg	milligrams
mL	milliliter
mm	millimeter
MO	Medical Officer
μM	micrometer
MTD	maximum tolerated dose
MTN	Microbicide Trials Network
NAAT	nucleic acid amplification test
ng	nanogram
NIAID	National Institute of Allergy and Infectious Diseases
NICHHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
nM	nanometer
NNRTI	non-nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OHRP	Office for Human Research Protections
pg	picograms
pH	potential hydrogen
PI	Principal Investigator
PK	pharmacokinetics
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development, Inc.
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PSP	Prevention Sciences Program
PSRT	Protocol Safety Review Team
PTID	participant identification
RNA	ribonucleic acid
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SCID	severe combined immunodeficiency
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SOP	standard operating procedure
SSP	study specific procedure(s)
STI	sexually transmitted infection
SUSAR	suspected, unexpected serious adverse reaction
TEAE	treatment emergent adverse event
UNAIDS	Joint United Nations Programme on HIV/AIDS
UPMC	University of Pittsburgh Medical Center
USA	United States of America
UTI	urinary tract infection
VR	vaginal ring
wt	wild-type

**MTN-029/ IPM 039**

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**MTN-029/ IPM 039**

**Phase 1 Pharmacokinetic Study of the Dapivirine Vaginal Ring in Lactating Women**

**INVESTIGATOR SIGNATURE FORM**

**Version 1.0**

**June 30, 2015**

**A Study of the Microbicide Trials Network**

**Funded by:**

Division of AIDS, US National Institute of Allergy and Infectious Diseases  
US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
US National Institute of Mental Health  
US National Institutes of Health

**IND Holder:**

International Partnership for Microbicides (IPM)

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, NICHD, IPM and other entities for review prior to submission, as required by the MTN Publication Policy.

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-029/ IPM 039

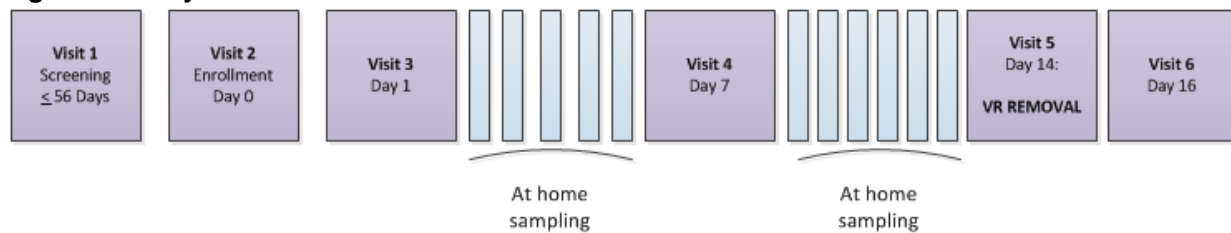
### Phase 1 Pharmacokinetic Study of the Dapivirine Vaginal Ring in Lactating Women

#### PROTOCOL SUMMARY

<b>Short Title:</b>	Phase 1 PK Study of the Dapivirine Vaginal Ring in Lactating Women
<b>Clinical Phase:</b>	Phase 1
<b>IND Sponsor:</b>	IPM
<b>Protocol Chair:</b>	Lisa Noguchi, PhD, CNM
<b>Protocol Co-Chair:</b>	Richard Beigi, MD, MSc
<b>Sample Size:</b>	Approximately 16 lactating women
<b>Study Population:</b>	Healthy lactating women, 18 years or older at screening, at least 6 weeks postpartum, who are able to produce breast milk but who are not breastfeeding
<b>Study Sites:</b>	Site(s) approved by the MTN Executive Committee
<b>Study Design:</b>	Phase 1, open-label study
<b>Study Duration:</b>	Each enrolled participant will be followed for approximately 2 weeks  Approximately 12-18 months for planned accrual and study duration
<b>Study Products:</b>	Dapivirine vaginal ring (VR)
<b>Study Regimen:</b>	Participants will receive a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine to wear for approximately 14 continuous days



**Figure 1: Study Visit Schedule**



**Primary Objective:**

1. To assess the pharmacokinetics of dapivirine vaginal ring used for 14 consecutive days in lactating women

**Primary Endpoints:**

1. Pharmacokinetics
  - Blood dapivirine levels
  - Breast milk dapivirine levels
  - Cervicovaginal fluid dapivirine levels

**Secondary Objectives:**

1. To assess safety and tolerability of dapivirine vaginal ring used for 14 consecutive days in lactating women
2. To assess adherence to dapivirine vaginal ring use in lactating women

**Secondary Endpoints:**

1. Safety and Tolerability
  - Grade 2 or higher genitourinary AEs
  - All Grade 3 or higher AEs

2. Adherence
  - Blood dapivirine levels and residual levels in returned VRs

**Exploratory Objective:**

1. Describe changes in vaginal microflora after 14 consecutive days of dapivirine vaginal ring use
2. Describe dapivirine anti-HIV activity in breast milk

**Exploratory Endpoints:**

1. Candidate biomarkers of vaginal microflora
2. Anti-HIV activity in breast milk

# 1 KEY ROLES

## 1.1 Protocol Identification

Protocol Title: Phase 1 Pharmacokinetic Study of the Dapivirine Vaginal Ring in Lactating Women

Protocol Number: MTN-029/IPM 039

Short Title: Phase 1 PK Study of the Dapivirine Vaginal Ring in Lactating Women

Date: June 30, 2015

## 1.2 Funders, Sponsor and Monitor Identification

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## **1.6 Study Implementation**

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## 2 INTRODUCTION

### 2.1 Microbicides and Human Immunodeficiency Virus (HIV) Prevention

In 2013, 2.1 million people became newly infected with HIV and 1.5 million lost their lives to acquired immunodeficiency syndrome (AIDS). Every hour, 50 young women are infected with HIV worldwide.<sup>1</sup> According to the Joint United Nations Programme on Human Immunodeficiency Virus-1(HIV)/AIDS (UNAIDS) Global Report, the estimated number of individuals living with HIV is 35 million globally. Given the high rates of HIV infection among women, female controlled prevention options remain a global priority. Women and girls continue to be affected disproportionately by HIV in sub-Saharan Africa, where women account for approximately 58% of people living with HIV; adolescent girls and young women account for a quarter of the new infections in this region.<sup>2</sup> The ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.

Unprotected heterosexual intercourse is currently the leading mode of HIV acquisition among women.<sup>2</sup> Correct and consistent use of latex condoms is one proven method of preventing HIV acquisition; however, condoms are widely regarded as inadequate prevention options for women, because many women are unable to negotiate condom use with their partners. The most widely available HIV prevention methods require the consent of the male partner. Thus, developing HIV prevention options that women can use remains a global concern. Vaginal microbicides, which are self-initiated and controlled, offer women a critically needed biomedical prevention tool that will complement existing HIV prevention strategies as well as future products being developed. With successful proof-of-concept that antiretroviral (ARV)-based microbicides reduce the risk of HIV-1 acquisition,<sup>3-5</sup> confirmatory work and further trials involving different ARV compounds, various formulations, and different dosing strategies, are required to provide options to end users and to improve upon the level of product effectiveness.

For a microbicide to be most effective, it is essential that it be used correctly and consistently, and be acceptable to the user. In addition, a product administered independently of anticipating sexual intercourse could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. Higher adherence to a product may translate into higher effectiveness of the product.<sup>3-5</sup> It is likely that products that can be applied less frequently or products that can remain *in situ* for an extended duration will be more acceptable and will achieve better adherence. Vaginal rings (VRs) that need to be replaced monthly may have benefits over other dosage forms that need to be used more frequently.

Multiple clinical trials have evaluated the safety of dapivirine in various formulations administered by various routes, including VRs, gels (vaginal administration) and pills (oral administration). These clinical trials support the favorable safety profile and

tolerability of dapivirine in general and specifically in vaginal delivery formulations. The dapivirine VR (Ring-004) is currently being evaluated for safety and efficacy in two Phase 3 clinical trials, IPM 027 (The Ring Study) and MTN-020 (ASPIRE). Both trials were initiated in 2012 and, as of April 2015, have completed enrollment and are currently following participants. Because the studies are ongoing, preliminary safety data are not yet available. Biannual Data and Safety Monitoring Board (DSMB) reviews have been ongoing for both trials and at no time has either DSMB expressed concerns regarding safety issues related to study product or trial participation. At the most recent DSMB review for ASPIRE (4 November 2014), it was recommended that the study continue, as planned and without modification, to its anticipated conclusion in June of 2015. The recommendation for The Ring Study at its most recent DSMB review (5 November 2014) was for the study to continue as planned.

Initiation of an open-label follow-on study to MTN-020 (MTN-025 or HOPE) will be contingent upon demonstration of the safety and efficacy of the product in MTN-020 (results are anticipated in Q4 of 2015).

## **2.2 Breastfeeding Women and HIV Prevention**

Extensive research has demonstrated the health benefits to infants who are exclusively breastfed during the first six months of life.<sup>2,3</sup> Breastfeeding is commonly practiced among women living in countries with a high prevalence of HIV infection, with the breastfeeding period typically extending for one to two years or more.<sup>24</sup> Women with multiple children may spend many years of their lives in serial periods of pregnancy and breastfeeding, sometimes with overlap between the two states. HIV prevention among breastfeeding women and their infants is of vital importance<sup>2</sup> as the postpartum period may be a time of increased HIV risk.<sup>6</sup> Further, a potentially higher probability of male unprotected sex outside of the primary partnership may increase a woman's risk.<sup>7</sup> Breastfeeding women, however, are commonly excluded from participation in clinical studies evaluating new agents for HIV prevention in adults due to the lack of sufficient safety and pharmacokinetic (PK) data in this population.<sup>8</sup> This exclusion impacts not only the availability of important data on this key population, but also impacts the power of any HIV prevention trial, as woman-years of follow-up are lost due to time off of study product. Thus, the thorough evaluation of investigational products for HIV prevention necessarily includes this population to enable accumulation of sufficient pre-licensure safety and PK data.

Due to the favorable safety profile of the dapivirine VR<sup>9</sup> and the importance of exploring the potential use of a dapivirine VR in this key demographic for HIV prevention, the MTN has proposed to move forward testing of the dapivirine VR in lactating women. This decision is further supported by the FDA's need for clinical trial data on the use of the dapivirine VR in lactating women to avoid placing a restriction on its use by this population, if the dapivirine VR is considered for market approval.<sup>10</sup>

## 2.3 Dapivirine Vaginal Ring (VR)

### 2.3.1 Description

Dapivirine (also known as TMC-120), a non-nucleoside reverse-transcriptase inhibitor (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>11</sup> The dapivirine matrix VR is a flexible ring containing 25 mg of drug substance dispersed in a platinum-catalyzed cured silicone matrix. When delivered via VR, dapivirine has demonstrated favorable safety and pharmacokinetic profiles as described below.

Dapivirine was originally developed by Janssen Research and Development (formerly Tibotec Pharmaceuticals Ltd.), a subsidiary of Johnson & Johnson, as an oral ARV compound for treatment of HIV/AIDS and was tested in Phase 1 and 2 clinical trials in more than 200 participants.<sup>12</sup> However, dapivirine is also a promising topical microbicide candidate due to its proven *in vitro* and *in vivo* efficacy and favorable safety profile as well as its physical and chemical properties. Dapivirine has potent activity against wild-type HIV-1 strains and strains harboring different resistance-inducing mutations. Dapivirine's ARV profile is superior to that of several other NNRTI drugs, including nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). Like other NNRTIs, *in vitro* tests have also shown that dapivirine is not active against HIV-2 and has little or no activity against common sexually transmitted infections (STI), therefore, it is not intended for use against HIV-2 or other STIs. Dapivirine does not have any contraceptive properties.<sup>13</sup> Detailed information on dapivirine is available in the Dapivirine VR Investigator's Brochure (IB).<sup>14</sup>

The International Partnership for Microbicides (IPM) has investigated a wide range of dosage formulations for the development of topical microbicide products, including vaginal gels, rings, films, tablets and soft gel capsules. The vaginal gel was the initial dosage form chosen for a dapivirine-based microbicide because the majority of previous microbicides evaluated in clinical trials were also vaginal gels. Therefore, a wealth of information was available on this dosage form. However, the dapivirine silicone elastomer VR has now been prioritized over all other dosage forms for the following reasons:

- Clinical trials have demonstrated sustained delivery of high levels of dapivirine throughout the cervicovaginal vault for up to 1 month;
- Since the VR is able to deliver drug for at least 1 month, the burden of user-dependent adherence is lower than for once daily products;
- Product acceptability studies and the experience gained from marketed VR products have established a high level of acceptance and adherence from women using VR with similar physical characteristics;
- The overall cost for the VR is relatively low;
- Minimal storage space is required for the VR when compared with once daily products.

Summaries of the safety and tolerability of dapivirine administered orally and vaginally as evaluated in clinical studies by IPM and Tibotec Pharmaceuticals can be found below.

### **2.3.2 Mechanism of Action**

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

### **2.3.3 Strength of Study Products**

The dapivirine VR (Ring-004) contains 25 mg of dapivirine. Ring-004 is a matrix VR in which the drug substance is dispersed in a platinum-catalyzed cured silicone.

## **2.4 Nonclinical Studies of Dapivirine**

### **2.4.1 *In Vitro* Studies of Dapivirine**

#### **Anti-HIV-1 Activity**

The antiviral 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. The 50% effective concentration (EC<sub>50</sub>) values ranged from 0.3 ng/mL (0.9 nM) against laboratory isolates to <33 ng/mL (<100 nM) against HIV-1 isolates encoding one or more known NNRTI resistance mutations.<sup>11, 13</sup>

The anti-HIV activity of dapivirine was also confirmed in an *ex vivo* model of human cervical explant cultures and a humanized severe combined immunodeficient (hu-SCID) mouse model.<sup>11, 13</sup> Pre-treatment of tissue with dapivirine for 2 or 24 hours inhibited HIV-1 infection when challenged with virus on Days 0, 2, 4 and 6 post drug removal. Dapivirine was also able to inhibit virus dissemination by migratory cells for up to 6 days post drug removal at concentrations as low as 10 µM (3.3 µg/mL) following treatment for 2 or 24 hours. In addition, dapivirine (32.9 ng/mL) was able to block transfer of free virus by migratory dendritic cells to indicator T-cells (IC<sub>50</sub>= 0.1 nM [0.03 ng/mL]).

#### **Resistance**

HIV-1 breakthrough in the presence of dapivirine was initially evaluated in studies in which cells were infected with wild-type HIV-1 laboratory strains at a high multiplicity of infection and in the presence of increasing concentrations of dapivirine. At dapivirine concentration of 40 nM, virus breakthrough occurred between 4 and 7 days; at 200 nM, breakthrough occurred between 7 and 10 days; and at 1 µM, virus breakthrough took up to 30 days to occur. In all cases, mutations were present. Virus that selected for 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 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<sub>LAI</sub>-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.

Experiments comparing the selection of resistant viruses following exposure to dapivirine with that following exposure to the NNRTIs UC781, MIV-160, nevirapine and efavirenz, showed that dapivirine demonstrated a high genetic barrier to resistance development in three viral isolates from subtypes B, C, and CRF02\_AG. Fully resistant viruses took 12 weeks to emerge, whereas reduced susceptibility to the NNRTIs UC781, efavirenz and nevirapine was detected within 5 weeks. Unlike UC781 and MIV-160, dapivirine did not select for mutations common to all three isolates, although the subtype C VI829 and CRF02\_AG MP568 viruses contained the mutations L100I and E138K. Other mutations selected under dapivirine pressure included E138Q, K101E, V108I, K103N, Y181C, V179M/E and F227Y.

To evaluate whether the presence of resistance mutations impaired replication fitness, p2/p7/p1/p6/PR/RT/INT-recombinant NNRTI-resistant viruses were constructed and viral growth evaluated. Only four out of 15 resistant viruses showed impairment in replicative fitness; however, one of them was a dapivirine-resistant form of VI829.

### **Cross-resistance**

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

### **Condom Compatibility**

Chemical compatibility studies with different dapivirine-containing gel formulations have been conducted on the following types of condoms:<sup>14</sup>

- Non-lubricated latex condoms (male condom);
- Silicone lubricated latex condoms (male and female condoms);
- Aqueous lubricated latex condoms (male condom);
- Polyurethane condoms with silicone lubricant (male and female condoms); and
- Nitrile condoms with silicone lubricant (female condom).

The results of condom compatibility testing indicate that dapivirine-containing vaginal gel formulations (0.05%) have no deleterious effects on the integrity of male or female condoms, as indicated by tensile condom properties tested pre- and post-treatment. Two clinical condom functionality studies (one with male condoms [IPM 029] and one with female condoms [IPM 033]) were conducted with a placebo VR (silicone elastomer ring containing no active ingredient). Results from both studies showed that the difference between the total clinical failure rate between condom use while using a VR and condom use while not using a VR was less than the pre-defined non-inferiority margins in both studies (3% for the male condom study and 8% for the female condom study). Condom use was safe and well tolerated during VR use.

## **2.5 Clinical Studies**

### **2.5.1 Clinical Studies of Dapivirine Vaginal Rings**

To date, a total of 27 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted:<sup>14</sup>

- Eight trials of dapivirine VRs (containing 25 mg and 200 mg loads); a total of 469 participants were assigned to receive dapivirine VRs,
- Eight trials of dapivirine vaginal gel; a total of 491 participants were assigned to receive dapivirine vaginal gel,
- Eleven trials of oral dapivirine; a total of 211 participants were assigned to receive oral dapivirine.<sup>11</sup>

## **Clinical Pharmacokinetics**

In clinical trials evaluating the use of VRs and vaginal gels to date, dapivirine concentrations in plasma have been very low (less than 2 ng/mL) or undetectable up to 84 days after drug exposure. Maximum plasma levels of dapivirine after vaginal administration in clinical trials were 1000-fold lower than maximum plasma concentrations after oral administration of dapivirine (e.g., dapivirine  $C_{max}$  after oral administration (300 mg b.i.d., for 14 days) was 2286 ng/mL).<sup>14</sup>

The clinical pharmacokinetic profile of Ring-004 dapivirine VR formulation evaluated in IPM 013 showed a rapid increase in plasma and vaginal fluid concentrations of dapivirine after ring insertion. The VR was used for approximately 56 or 57 days. Maximal dapivirine plasma concentrations were achieved in plasma by Day 7 post VR insertion and maximal dapivirine concentrations in cervicovaginal fluids were achieved between Day 1 and Day 14 post VR insertion. Dapivirine concentrations decreased steadily over the remainder of a 28-day or 35-day ring use period. Plasma dapivirine concentrations did not exceed 1 ng/mL, and were therefore well below concentrations at the maximum tolerated dose (MTD) for multiple oral dapivirine doses (300 mg b.i.d. for 14 days; plasma  $C_{max}$  = of 2286 ng/mL). For dapivirine in cervivaginal fluids, the highest dapivirine concentration was observed in the area where the ring was placed, followed by the cervix, with the lowest concentrations near the introitus.

Data from post-use analysis of residual levels of dapivirine in Ring-004 (IPM 015, in which a ring containing dapivirine 25 mg was inserted once every 28 days over a 12-week period) indicate that, on average, 4 mg of dapivirine were released over approximately one month of ring use. The mean remaining amounts of dapivirine in the used VR were similar for Weeks 4, 8 and 12 (post-insertion), at 21.09 mg, 21.54 mg and 21.84 mg, respectively. No clear relationship (neither linear nor exponential) was observed between the residual amount of dapivirine and corresponding plasma concentrations (i.e., at scheduled ring removal). Dapivirine plasma concentrations below approximately 200 pg/mL were generally associated with above-average ring residual amounts, while plasma concentrations above 200 pg/mL were generally associated with relatively constant residual levels (between approximately 20 and 22 mg).

## **Safety**

**Table 1: Clinical Phase I/II Trials of Dapivirine Vaginal Rings**

Trial Details			Number of Participants				
Trial Number	Description	Country	Ring-001 reservoir (200 mg)	Ring-002 reservoir (25 mg)	Ring-003 matrix* (25 mg)	Ring-004 matrix** (25 mg)	Placebo Ring
IPM 001	Safety and PK in women; 7 days	Belgium	12	--	--	--	12 (crossover)
IPM 008	Safety and PK in women; 7 days	Belgium	--	10	--	--	3
IPM 013	Safety and PK in women; 56/57 days	Belgium	--	--	--	36	12

Trial Details			Number of Participants				
Trial Number	Description	Country	Ring-001 reservoir (200 mg)	Ring-002 reservoir (25 mg)	Ring-003 matrix* (25 mg)	Ring-004 matrix** (25 mg)	Placebo Ring
IPM 015	Safety and PK in women; 84 days	Multiple Countries in Sub-Saharan Africa	--	--	--	140	140
IPM 018	Safety and PK in women; 28 days	Belgium	--	8	8	--	8
IPM 024	Safety and PK in women; 28 days	Belgium	--	--	--	8	8
MTN-013/ IPM 026***	Safety and PK in women	United States	--	--	--	12	12
IPM 028	Drug-drug Interaction (dapivirine VR-miconazole nitrate); 28 days	Belgium				36	0
IPM 034	Safety and PK in women; 7, 14, 28, 56, or 84 days	Belgium				40	0
TOTAL			12	18	8	272	195

\*Tin-catalyzed matrix ring.

\*\*Platinum-catalyzed matrix ring

\*\*\*MTN-013/ IPM 026 was the first in human clinical trial evaluating VRs containing maraviroc alone, dapivirine alone or a combination of the two (dapivirine/maraviroc) as compared to placebo. The dapivirine VR arm included 12 participants. It should be noted, however, that the dapivirine VR was similar to Ring-004, but of slightly different composition.

Across all clinical trials conducted in healthy participants evaluating multiple ring configurations, the dapivirine VR was generally safe and well-tolerated.<sup>15</sup> IPM has conducted a review of aggregate safety information and has identified vaginal candidiasis as a possible adverse drug reaction caused by dapivirine VR use. The highest reported severity of vaginal candidiasis observed across all studies was a Grade 2, reported in women using the Ring-004 dapivirine VR.

The first dapivirine VR tested in humans, Ring-001, consisted of two reservoir cores containing a total of 200 mg 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 center in Belgium (IPM 001).<sup>16</sup> Women used the placebo ring for 7 days followed by the dapivirine ring for seven days. No serious adverse events (SAEs) were reported during the trial, and few treatment-emergent adverse events (TEAEs) were observed. The Dapivirine Ring-001 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 containing 25 mg dapivirine, was tested in a Phase 1, randomized, placebo-controlled trial conducted in 13 healthy, sexually abstinent, HIV-uninfected women at a single research center in Belgium (IPM 008).<sup>17</sup> Ten women used the Dapivirine Ring-002 and three women used a placebo ring for seven continuous days. No SAEs were reported during the trial and

few TEAEs were observed. The trial results showed that the Dapivirine Ring-002 was safe in healthy participants.

Ring-003, a dapivirine matrix VR 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 center in Belgium (IPM 018). 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 determined to be definitely or probably related to the ring, and similar percentages of participants in the dapivirine and placebo ring groups had TEAEs considered possibly related to the ring.

Ring-004, the current formulation, is a dapivirine matrix VR containing 25 mg of drug substance dispersed in a platinum-cured silicone matrix. It has been evaluated in five completed clinical trials.<sup>14</sup>

The first clinical trial of Ring-004, IPM 024, was conducted in Belgium and enrolled 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 VR group. No AEs were judged by the investigator to be related to the study agent. Most dapivirine VR group participants, 87.5% (7/8), experienced at least one TEAE. Of the women in the dapivirine VR group who experienced a TEAE, 50% (4/8) reported headache. Of the participants using dapivirine VRs, 50% experienced Grade 1 or Grade 2 metrorrhagia, 38% experienced vulvovaginal discomfort and 25% experienced nasopharyngitis. One participant experienced a Grade 1 vaginal hemorrhage in the dapivirine VR group.

IPM 013 was a Phase I, randomized, double-blind, placebo-controlled trial conducted over 3 months at one research center in Belgium (IPM 013).<sup>14</sup> Forty-eight healthy, HIV-negative, sexually active women between 18 to 40 years of age were assigned in groups of eight to one of two groups, Group A or Group B (unblinded assignment). Within each group, participants were randomized in a blinded manner, in a 3:1 ratio, to either the dapivirine ring or placebo ring, for a total of four treatment arms. In Group A, the first vaginal ring was removed on Day 28, and a second vaginal ring inserted after 3 days, on Day 31, for another 28 days. In Group B, the first vaginal ring was removed on Day 35, and a second vaginal ring was inserted after 3 days, on Day 38, for another 21 days. A third vaginal ring was inserted immediately following removal of the second ring on Day 59, and was worn for 24 hours. No SAEs were reported during the trial. One participant discontinued the trial due to a TEAE of generalized pruritus; the event was not considered serious, of Grade 2 (moderate) intensity, and regarded by the investigator as possibly related to use of the dapivirine ring. No TEAEs were assessed by the investigator as definitely or probably related to the dapivirine ring, and a similar percentage of participants in the dapivirine and placebo ring groups had TEAEs considered to be possibly related to the vaginal ring.

IPM 015 was a double-blind, randomized, placebo-controlled Phase 1/2 trial conducted at 10 research centers in Kenya, Malawi, Tanzania and South Africa. The trial was performed in 280 healthy, HIV-negative women who inserted a vaginal ring once every 21-35 days over a 12-week period. Five SAEs occurred during the trial, of which four occurred in placebo participants.<sup>18</sup> None of the SAEs were judged to be related to product. No TEAEs led to premature discontinuation of ring use. One participant in the dapivirine treatment group reported Grade 3 tonsillitis, which was unrelated to the investigational product. Four participants in the placebo treatment group reported one instance each of bronchiectasis (Grade 3), peritonsillar abscess (Grade 3), suicide attempt (Grade 3), and hemopneumothorax (Grade 4). The hemopneumothorax was caused by a physical assault; this event was unrelated to the investigational product. A chemical pregnancy was reported for one participant in the placebo ring group who discontinued product use, but continued to attend the research center for safety evaluations and completed the remainder of trial visits. In IPM 015, two vaginal bleeding events were reported; both occurred in the placebo ring arm. Apart from the latter two events, chemical pregnancy and hemopneumothorax, none of the SAEs or TEAEs led to premature discontinuation of ring use.

IPM 028, the fourth trial of Ring-004 was a Phase I open-label, randomized, 3-period, 2-sequence, cross-over trial, to assess the drug-drug-interaction potential between Ring-004 and miconazole nitrate, administered as a single dose (1200 mg) vaginal capsule (Gyno-Daktarin<sup>®</sup>) in HIV-negative women, 18 to 40 years of age.<sup>14</sup> The trial was conducted at a Phase I unit in Belgium and enrolled 36 women, randomly assigned to one of two treatment sequences, ABC or BAC, during which they received three treatments, each separated by a washout period of 3 weeks: Treatment A = Dapivirine Vaginal Ring-004 inserted for 28 days; Treatment B = Dapivirine Vaginal Ring-004 inserted for 28 days along with a single dose of miconazole nitrate on Day 0; Treatment C = a single dose of miconazole nitrate inserted on Day 0. One SAE (fracture of the right acetabulum) was reported in a participant during the washout period who had been assigned to initial treatment with the dapivirine ring and miconazole vaginal capsule (Treatment B). The event was assessed as severe (Grade 3) and regarded by the investigator as unrelated to the IP. One TEAE was considered by the investigator as related to IP use during the trial. The participant was enrolled in Treatment Sequence ABC and experienced moderate (Grade 2) vulvovaginal candidiasis during the ring use period of Treatment A, two days before the scheduled ring removal. Based on all safety evaluations performed, no overall clinically significant differences were observed between treatment with the dapivirine vaginal ring alone, in co-administration with miconazole, or miconazole alone.

IPM 034, the fifth trial of Ring-004 was a Phase I open-label, parallel group trial, to assess the release profile of Ring-004 over extended periods of ring use in HIV-negative women, 18 to 40 years of age. The trial was conducted at a Phase I unit in Belgium and enrolled 40 women in five groups (Groups A, B, C, D and E) of eight women each. Each woman was administered one dapivirine ring and instructed to wear the ring continuously for a period of 7, 14, 28, 56, or 84 days (1, 2, 4, 8, or 12 weeks). One SAE (thoracic vertebral fractures following a motor vehicle accident) was reported

in a participant using the dapivirine ring in Group C. The event was assessed as severe (Grade 3) and regarded by the investigator as unrelated to the IP. Product-related TEAEs were reported for four women during the trial of whom three experienced mild vaginal discharge (one woman with a 56-day ring use period and two women with an 84-day ring use period) and one experienced moderate bacterial vaginosis (84-day ring use period). Based on all safety evaluations performed during the trial, no overall clinically significant differences were observed between the different ring use periods.

MTN-013/IPM 026, a Phase 1 safety and pharmacokinetics study of dapivirine VR, maraviroc VR, dapivirine/maraviroc VR and placebo VR, enrolled approximately 48 women between the ages of 18-40. The participants were randomized in a 1:1:1:1 ratio to one of the four products, with all groups assigned to 28 days of continuous study vaginal ring use. Over the course of 52 days, 14 follow-up visits occurred. No statistically significant difference in the number of participants with genitourinary AEs was noted between placebo arm and any other treatment arms. Twenty-two women experienced 33 grade 1 and one grade 2 related genitourinary AEs.<sup>19</sup> Two grade 2 AEs were determined to be related to study product. At Day 28, dapivirine vaginal fluid levels were 14.9 µg/mL in women assigned to the dapivirine only ring.

In March of 2012, IPM 027, also known as The Ring Study, was initiated. IPM 027 is a randomized, double-blind, placebo-controlled efficacy and long-term safety study that has enrolled 1959 healthy, HIV-uninfected women, ages 18-45. The study is being conducted in South Africa and Uganda. Study participants will use either the dapivirine ring or the placebo ring every four weeks over approximately two years. The main goals of The Ring Study are to evaluate the long-term safety and efficacy of the dapivirine ring for the prevention of HIV-1 as compared to a placebo ring, when used by healthy, HIV-negative women over a two-year period. Additional goals include measuring the incidence of curable STIs, HIV-2 and pregnancy; monitoring ring acceptability (how well women like using the ring) and adherence (if women use the ring as intended) as reported by the study participants; and tracking the development of any HIV-1 drug resistance in participants who become HIV positive during the study. The study is anticipated to conclude in 2015 or 2016.

MTN-020, A Study to Prevent Infection with a Ring for Extended Use (ASPIRE), is a Phase 3 clinical trial designed to assess the efficacy and safety of a ring containing 25 mg of dapivirine for the prevention of HIV-1 acquisition in women. The double-blind, randomized controlled trial is being conducted in HIV-uninfected women, between the ages 18 and 45. A total of 2629 women from Malawi, South Africa, Uganda, and Zimbabwe have enrolled in the trial. Participants replace the ring monthly for a minimum of one year. MTN-020 aims to determine the safety and efficacy of the dapivirine ring in preventing HIV-1 infection among healthy, sexually active, HIV-uninfected women when inserted vaginally once every 4 weeks. Additional goals of MTN-020 include the assessment of participant acceptability and adherence to the investigational product, HIV-1 drug resistance mutations among participants who acquire HIV-1 infection, and establishing steady state drug concentrations in the study population. Results are anticipated in 2015.

## **2.6 Behavioral Studies**

### **2.6.1 Acceptability of Dapivirine VR**

IPM 011 assessed the acceptability of the dapivirine VR and the placebo VR in 170 women. The trial was conducted across multiple sites in Tanzania and South Africa. The study participants found the ring to be very comfortable (95%), very easy to insert (94%) and remove (92%), and rarely were the rings felt during daily activities. All questionnaire respondents, when asked if they would be willing to use the vaginal ring if shown to be effective for HIV prevention, replied that they would use the VR.<sup>20</sup>

In IPM 015, at Week 12, 97% of African women reported that the dapivirine VR was comfortable and that they were willing to use the VR if it was found to be effective. Women preferred to wear the VR every day (97%) and reported that the ring did not interfere with their daily activities (89%). In terms of the male partner acceptability, 63% of women reported that their partner did not feel the ring during sex. Of those participants who reported that their partner felt the ring, only 1% reported that this might be or definitely was a problem.<sup>18</sup>

### **2.6.2 Adherence of Dapivirine VR**

In IPM 011, 11% of the women experienced expulsions or removal, with the most common reason being 'menses related'. In the majority of cases (64%), the VR was washed and re-inserted.<sup>20</sup>

In IPM 015, perfect adherence was reported by 92% of the female participants. Perfect adherence was defined as never having the VR out for more than an entire day. Of the women who reported that the ring was out, the most common activity for expulsion was urination/defecation. The most common reason reported by participants for VR removal was to clean the VR. As the study progressed, more women reported removing the VR prior to sexual intercourse, 17% at week 2 and 36% by week 12.<sup>18</sup>

## **2.7 Rationale for Study Design**

### **2.7.1 Study Design**

The design of MTN-029/IPM039, a clinical study of dapivirine VR in lactating women, will provide data on the PK profile of dapivirine drug in lactating women who have completed weaning when administered in VR formulation. It evaluates dapivirine levels in both plasma and breast milk and the amount of drug transferred into breast milk during the participant's 14 days of use. The trial design limits the length of study product exposure to ensure that participants continue to lactate in sufficient quantities for PK analysis. It is important to note that MTN-029/IPM 039 will not establish the half-life of dapivirine, as doing so would require women to maintain a breast milk supply following



weaning for 21 to 28 days, a requirement which could negatively impact participant recruitment and retention. A larger trial enrolling mother-infant pairs for a longer follow-up period may be better suited to address this research objective. Infant PK sampling will also not be performed in this study (since the infant will not receive breast milk produced after ring use is initiated); therefore, the systemic dapivirine exposure of breastfed infants cannot be measured in this study design. However, total dose exposure can be roughly estimated based on levels measured in maternal breast milk; PK data will allow for determination of the concentration-time profiles and subsequent PK parameters of dapivirine to be calculated based on maternal blood and milk samples. Data will be pooled across participants to provide this estimate. The participant population includes lactating women and the study design includes frequent collection of corresponding maternal blood and milk samples following insertion of a dapivirine VR. Further, total lipids will be measured from breast milk samples to help characterize the variability.

The current study is designed to avoid exposing infants to dapivirine via breast milk, particularly as the quantity of dapivirine that may be transferred into breast milk is yet unknown. PK parameters will only be evaluated in lactating women who have stopped breastfeeding their infants. This design is typically preferred for studies that include newly approved drugs (especially for drugs with no available pediatric data), short-term or acute maternal dosing, and unknown risk of exposure to the breastfed child.<sup>10</sup> Results from this study may support a future, more complex study design that includes breastfeeding mother-infant pairs, therefore including potential exposure to drug via breast milk in infants. Drug and metabolite characteristics that favor selection of the sequential or step-wise approach include the following:

- High lipophilicity (weak bases)
- Presence in milk
- Predictions that drug is present in milk
- Knowledge of a class effect

As mentioned previously, the MTN-029/IPM039 study will contribute data needed for product labeling that would not restrict use of the dapivirine VR by lactating women, if the dapivirine VR is considered for market approval.

### **2.7.2 Study Hypotheses**

We hypothesize the following:

- Dapivirine will be detectable at low levels in breast milk, and only in a minority of participants
- Blood dapivirine levels will be detectable at low levels in all women
- Continuous exposure via use of the dapivirine VR by lactating women for 14 days will be well-tolerated and not associated with significant toxicity in women

## **3 OBJECTIVES**

### **3.1 Primary Objective**

1. To assess the pharmacokinetics of dapivirine VR used for 14 consecutive days in lactating women

### **3.2 Secondary Objectives**

1. To assess safety and tolerability of dapivirine vaginal ring used for 14 consecutive days in lactating women
2. To assess adherence to dapivirine vaginal ring use in lactating women

### **3.3 Exploratory Objectives**

1. Describe changes in vaginal microflora after 14 consecutive days of dapivirine vaginal ring use
2. Describe dapivirine anti-HIV activity in breast milk

## **4 STUDY DESIGN**

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

MTN-029/IPM 039 is a Phase 1, open-label pharmacokinetic study of the dapivirine vaginal ring in lactating women.

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

#### **Primary Endpoints:**

1. Pharmacokinetics
  - Blood dapivirine levels
  - Breast milk dapivirine levels
  - Cervicovaginal fluid dapivirine levels

#### **Secondary Endpoints:**

1. Safety and Tolerability
  - Grade 2 or higher genitourinary AEs
  - All Grade 3 or higher AEs

2. Adherence
  - Blood dapivirine levels and levels in returned VRs

### **Exploratory Endpoints:**

1. Candidate biomarkers of vaginal microflora
2. Anti-HIV activity in breast milk

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

Approximately 16 healthy women, who are over the age of 18, at least 6 weeks postpartum, and able to produce breast milk.

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

Accrual is expected to be completed in approximately 12-18 months.

### **4.5 Expected Duration of Participation**

Each enrolled participant will be followed for approximately 2 weeks. Each participant will complete a total of 6 visits. Visits may be completed within specified windows around target dates. Detailed information regarding visit windows will be described in the MTN-029/IPM 039 SSP Manual.

### **4.6 Site**

Site(s) selected by the MTN Executive Committee will participate in MTN-029/IPM 039.

## **5 STUDY POPULATION**

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

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

#### **5.1.1 Recruitment**

Study site staff will recruit potential participants from a variety of locations/sources, including, clinical care and community site(s), prenatal and postnatal care clinics, etc., using IRB-approved materials. Recruitment materials will be approved by site Institutional Review Boards (IRBs) prior to use. Site community representatives should

advise on these materials before they are submitted to the IRB/Ethics Committee (EC) for review. Community education strategies, including group sessions, may be employed as part of participant/partner outreach. Recruitment materials and processes will not encourage women to discontinue breastfeeding.

### **5.1.2 Retention**

Once a participant is enrolled into MTN-029/IPM 039, the study site will make every effort to retain the participants in follow-up to minimize possible bias associated with loss-to-follow-up. An average retention rate of 95% will be targeted across sites. The study site(s) will establish and follow standard operating procedures (SOPs) for participant retention.

### **5.2 Inclusion Criteria**

Women must meet all of the following criteria (by self-report, unless otherwise indicated) to be eligible for inclusion in the study:

1. Age 18 or older at screening as verified per site SOP
2. Per participant report, at least 6 weeks postpartum at Enrollment
3. Willing and able to provide written informed consent to be screened for and take part in the study
4. Willing and able to provide adequate locator information, as defined in site SOP
5. Willing and able to communicate in spoken and written English
6. HIV-1/2 uninfected at Screening and Enrollment, per applicable algorithm in Appendix II and willing to receive HIV test results

Note: HIV-1/2 screening may be omitted at Enrollment if the time between Screening and Enrollment is  $\leq$  30 days

7. Prior to Enrollment, breastfeeding of child has stopped
8. Participant has no intention of providing expressed breast milk to her child(ren) or to others for consumption after initiation of study product

*Note: Providing stored breast milk to child(ren) that has been expressed prior to study product exposure is not exclusionary*

9. Willing and able to express breast milk at least twice daily for the duration of study drug exposure

10. Per participant report, using an effective method of contraception at Enrollment, and intending to continue the use of an effective method for the duration of study participation. Effective methods for MTN-029/IPM 039 include: hormonal methods (except contraceptive VRs), intrauterine device (IUD) inserted at least 28 days prior to enrollment, engages in sex exclusively with women, sterilized (self or partner), or sexually abstinent for the past 90 days
11. Women over the age of 21 (inclusive) must have documentation of a satisfactory Pap within the past 3 years 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 the Severity of Adult and Pediatric Adverse Events, Version 1.0, November 2007), or satisfactory evaluation with no treatment required of Grade 1 or higher Pap result
12. At Screening, participant states a willingness to refrain from receptive sexual activity (including penile-vaginal intercourse, anal intercourse, receptive oral intercourse, finger stimulation) and from inserting any non-study objects into the vagina (including tampons, sex toys, female condoms, diaphragms, menstrual cups, cervical caps or any other vaginal barrier method, etc.), for 24 hours prior to each clinic visit.
13. At Screening, participant states a willingness to refrain from the use of vaginal products, including, spermicides, lubricants, contraceptive VRs, douches, vaginal medications, etc., for the duration of study participation
14. Per participant report at Screening and Enrollment, agrees not to participate in other research studies involving drugs, medical devices, vaginal products, vaccines or breast milk sampling for the duration of study participation

Note: Participation in observational studies is not exclusionary

### **5.3 Exclusion Criteria**

Women who meet any of the following criteria (by self-report, unless otherwise indicated) will be excluded from the study:

1. Participant report of any of the following:
  - a. History of adverse reaction to any component of dapivirine VR
  - b. Participation in investigational drug or device trial within 30 days prior to the Enrollment Visit (Day 0)
  - c. Use of vaginal medication(s) 5 days prior to Enrollment (Day 0)
  - d. Complication of lactation requiring treatment, e.g., mastitis

2. At the time of Screening and Enrollment, clinical evidence of milk supply less than 1 ounce per expression
3. 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
4. Grade 2 or higher AST/ALT at Screening Visit:

Note: Otherwise eligible participants with an exclusionary AST/ALT may be retested during the screening process.

5. Positive urine pregnancy test at screening or enrollment
6. Diagnosed with urinary tract infection (UTI) at Screening or Enrollment

Note: Otherwise eligible participants diagnosed with UTI during screening are offered treatment and may be enrolled after completing treatment and all symptoms have resolved.

7. Diagnosed with an STI or a reproductive tract infection (RTI) requiring treatment per current Centers for Disease Control and Prevention (CDC) guidelines at Screening or Enrollment

*Note: Otherwise eligible participants diagnosed during screening with an STI/RTI requiring treatment per CDC guidelines — other than asymptomatic bacterial vaginosis (BV) and asymptomatic candidiasis — are offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 56 days of obtaining informed consent for screening, the participant may be enrolled. Genital warts requiring treatment also must be treated prior to Enrollment. Genital warts requiring therapy are defined as those that cause undue burden or discomfort to the participant, including bulky size, unacceptable appearance, or physical discomfort.*

8. On pelvic exam, any of the following findings:
  - a. Incomplete postpartum involution of the uterus
  - b. Clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff)

*Note: Genital bleeding clinically assessed to be expected is not exclusionary, including cervical bleeding associated with speculum insertion and/or specimen collection and irregular uterine bleeding associated with contraceptive changes or return of menses postpartum judged to be within the range of normal according to the clinical judgment of the IoR/designee.*

*Note: Otherwise eligible participants with exclusionary pelvic findings may be enrolled after the findings have improved to a non-exclusionary severity grading or resolved. If improvement to a non-exclusionary grade or resolution is documented within 56 days of providing informed consent, the participant may be enrolled.*

9. Use of oral and/or vaginal preparations of antibiotic or antifungal medications within 5 days of Enrollment
10. At Screening or Enrollment, any social or medical condition that, in the investigator's opinion, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

#### **5.4 Co-enrollment Guidelines**

As indicated in Section 5.2, participants must not take part in other research studies involving drugs, medical devices, vaginal products, vaccines, or breast milk sampling after the Screening Visit and while taking part in MTN-029/IPM 039 unless approved by the Protocol Safety Review Team (PSRT) and Protocol Chair. Participation in the following types of studies may be allowed at the discretion of the IoR/designee after consultation with the Protocol Chair and PSRT:

- Participants may take part in MTN ancillary studies
- 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 pregnancy registries

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-029/IPM 039, 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 receive a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine to wear continuously for approximately 14 days.

### **6.2 Administration**

An IoR/authorized clinician will insert the study VR at the site at the Enrollment Visit. Site staff will counsel participants in VR product use, including refraining from removing the ring (except as directed), and instructions for re-insertion in case of accidental ring expulsion, etc. Additional details will be provided in the MTN-029/IPM 039 SSP Manual.

### **6.3 Study Product Formulation**

The study VR is an off-white, flexible ring containing 25 mg of dapivirine dispersed in a platinum-catalyzed-cured silicone matrix. 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 for at least 28 days.

Dapivirine 0.3125% (w/w) is dispersed in a flexible, opaque, cured silicone VR delivery device. The VR will contain 25 mg of dapivirine. The dapivirine VR optimally should be stored in the site pharmacy at 77°F, with excursions between 59°F to 86°F.

### **6.4 Supply and Accountability**

IPM (Silver Spring, MD) will oversee the manufacture of the study VRs and analyze/release the rings under Good Manufacturing Practices (GMP). Study VRs will ship directly to the Clinical Research Site (CRS) Pharmacist of Record (PoR).

The PoR is required to maintain a complete record of all study product received. The procedures to be followed are provided in the MTN-029/IPM 039 Pharmacist Study Product Procedures Manual.

All study product dispensed to a participant must be documented by the clinic staff when it is returned. This includes a ring that is brought back to the clinic by the participant and any ring removed at the clinic visit. Any study product not returned must also be documented by the clinic.

#### **6.4.1 Storage and Dispensing**

Study VRs 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. Dispensing takes place on the day of enrollment. The pharmacist will dispense one ring at the enrollment visit. If a participant requires an additional ring for any reason she will be required to attend the clinic for an interim visit.

#### **6.4.2 Retrieval of Study Product**

It is expected that participants will return the VR at the Visit 5-Day 14: Ring Removal Visit. If the participant has removed the VR prior to the visit, they will be instructed to return the VR as soon as possible or at her next clinic visit. If the VR is not returned at the final clinic visit, site staff members will make every effort to encourage participants to return the VR as soon as possible. Attempts by study staff to retrieve the VR from the participant must be documented. The VR must be retrieved within 3 days following either the final clinic visit or permanent discontinuation from the study. The VR must be retrieved (optimally within 24 hours) and returned to the study site (clinic) when study product use is permanently discontinued for HIV seroconversion. If the vaginal ring is not returned within these time frames the MTN-029/IPM 039 PSRT must be notified.



## **6.5 Concomitant Medications**

Enrolled study participants may use concomitant medications during study participation. All concomitant medications 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.

## **6.6 Use of Intravaginal Medications and Practices**

The use of vaginal products, including, spermicides, lubricants, contraceptive VRs, douches, vaginal medications, etc., is prohibited. Receptive sexual activity (including penile-vaginal intercourse, anal intercourse, receptive oral intercourse, finger stimulation) and inserting any non-study objects into the vagina (including tampons, sex toys, female condoms, diaphragms, menstrual cups, cervical caps or any other vaginal barrier method, etc.), is permitted, except for 24 hours prior to clinic visits.

Use of intravaginal medications and practices will be captured on CRFs. Study participants will be asked about their sexual activity and practices at each clinic visit during which PK samples are collected.

## **6.7 Condoms**

Condoms will be provided to study staff for distribution to participants. Latex-free condoms will be provided to participants who cannot tolerate latex. Please reference the MTN-029/IPM 039 SSP Manual for additional details on condoms to be provided ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)).

# **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-029/IPM 039 SSP Manual available at [www.mtnstopshiv.org](http://www.mtnstopshiv.org).

## **7.1 Pre-screening**

Potential participants will be sought at 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 site in the absence of written informed consent, provided the information is collected in such a manner that it cannot be linked

to participant identifiers. Procedures and documentation will comply with local IRB requirements.

## 7.2 Visit 1- Screening Visit

A Screening Visit may take place up to 56 days prior to the Enrollment Visit (Day 0). Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed consent for screening will be obtained before any screening procedures are initiated. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined.

**Table 2: Visit 1- Screening Visit**

<b>Screening Visit</b>	
<b>Component</b>	<b>Procedure/Analysis</b>
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Obtain Informed consent</li> <li>• Assign a unique Participant Identification (PID) number</li> <li>• Assess eligibility</li> <li>• Demographic information</li> <li>• Collect locator information</li> <li>• Provide Reimbursement</li> <li>• Schedule next visit/contact*</li> </ul>
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>• Counseling on breast milk production maintenance*</li> <li>• HIV pre- and post-test counseling</li> </ul>
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Medical eligibility information (including exclusionary medical conditions and medications)</li> <li>• Medical history (e.g., review medical records, childbearing and lactation history)</li> <li>• Concomitant medications</li> <li>• Physical exam</li> <li>• Pelvic exam</li> <li>• Breast exam</li> <li>• Treatment for reproductive tract infection (RTI)/urinary tract infection (UTI), STIs or mastitis*</li> <li>• Provision of contraception and contraception counseling*</li> <li>• Disclosure of available test results</li> </ul>

<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• hCG</li> <li>• Urine dipstick/culture*</li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• HIV-1 serology</li> <li>• AST/ALT</li> <li>• Syphilis serology if not documented within past year</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>• Cervicovaginal NAAT for GC/CT</li> <li>• Trichomonas test</li> <li>• Pap smear interpretation<sup>^</sup></li> <li>• Wet prep &amp; vaginal pH*</li> <li>• Herpes culture*</li> </ul>
	<b>Breast</b>	<ul style="list-style-type: none"> <li>• Breast milk sample for eligibility</li> </ul> <p>Note: The breast milk collected for eligibility may also serve as the baseline sample to be stored.</p>

\* if indicated, ^ To be performed if a participant (over the age of 21) is unable to provide documentation of a satisfactory Pap smear within 3 years prior to enrollment

### 7.3 Visit 2- Enrollment (Day 0)

The Enrollment Visit must be completed within 56 days of the Screening Visit. Menses must not coincide with Study Visits 2-6, therefore participant's menstrual cycle must be considered when scheduling Visit 2- Enrollment (Day 0).

**Table 3: Visit 2- Enrollment (Day 0)**

<b>Visit 2- Enrollment (Day 0)</b>	
<b>Component</b>	<b>Procedure/Analysis</b>
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Assess and confirm eligibility</li> <li>• Review/update locator information</li> <li>• Provide reimbursement</li> <li>• Schedule next visit/contact*</li> </ul>
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>• Protocol adherence counseling (i.e., VR use instructions, counseling on collection/storage of breast milk at home, etc.)</li> <li>• Sexual practices assessment</li> <li>• HIV pre- and post-test counseling and referral for repeat testing</li> </ul> <p><i>Note: May be omitted if fewer than 30 days has passed between the Screening and Enrollment Visits</i></p>
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Medical eligibility information (including exclusionary medical conditions and medications)</li> <li>• Review/update medical history (e.g., review medical records, childbearing and lactation history)</li> <li>• Review/update concomitant medications</li> <li>• Physical exam</li> <li>• Pelvic exam</li> <li>• Breast exam</li> <li>• Digital exam by clinician to check VR placement</li> <li>• Treatment for reproductive tract infection (RTI)/urinary tract infection (UTI), STIs or mastitis*</li> <li>• Provision of contraception and contraception counseling*</li> <li>• Disclosure of available test results</li> </ul>

Visit 2- Enrollment (Day 0)		
Component		Procedure/Analysis
Laboratory	Urine	<ul style="list-style-type: none"> <li>• hCG</li> <li>• Urine dipstick/culture*</li> <li>• NAAT for GC/CT*</li> </ul>
	Blood	<ul style="list-style-type: none"> <li>• HIV-1 serology <i>Note: May be omitted if fewer than 30 days has passed between the Screening and Enrollment Visits</i></li> <li>• Plasma archive</li> <li>• Syphilis serology*</li> <li>• Blood DPV levels (Target: Pre-insertion, hr 3 and hr 6)</li> </ul>
	Pelvic	<ul style="list-style-type: none"> <li>• Pap smear interpretation<sup>^</sup></li> <li>• Trichomonas test*</li> <li>• Wet prep &amp; vaginal pH*</li> <li>• Herpes culture*</li> <li>• Vaginal biomarkers</li> <li>• Quantitative vaginal culture</li> <li>• Vaginal Gram stain</li> <li>• CVF DPV levels (Target: Pre-insertion, hr 3 and hr 6)</li> </ul>
	Breast	<ul style="list-style-type: none"> <li>• Breast milk for eligibility <i>Note: The breast milk collected for eligibility may also serve as the pre-insertion samples listed below.</i></li> <li>• Breast milk for DPV levels and lipids (Target: Pre-insertion, hr 3 and hr 6)</li> <li>• Breast milk for anti-viral activity (Target: Pre-insertion, hr 3 and hr 6)</li> </ul>
Study Product/Supplies		<ul style="list-style-type: none"> <li>• Provision of study VR</li> <li>• Insertion of one study VR and VR use instructions</li> <li>• Supplies for breast milk collection</li> </ul>

\* if indicated ^ To be performed if a participant (over the age of 21) is unable to provide documentation of a satisfactory Pap smear within 3 years prior to enrollment

## 7.4 Follow-up Visits

### 7.4.1 Visit 3- Day 1

Table 4: Visit 3- Day 1

Visit 3- Day 1		
Component	Procedure/Analysis	
<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/contact</li> </ul>	
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>HIV pre- and post-test counseling*</li> <li>Protocol adherence counseling (i.e., VR use instructions, counseling on collection/storage of breast milk at home, etc.)</li> <li>Sexual practices assessment</li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>Review/update medical history</li> <li>Review/update concomitant medications</li> <li>Physical exam*</li> <li>Breast exam*</li> <li>Pelvic exam</li> <li>Digital exam by clinician to check VR placement*</li> <li>Treatment for reproductive tract infection (RTI)/urinary tract infection (UTI), STIs or mastitis*</li> <li>Provision of contraception and contraception counseling*</li> <li>Disclosure of available test results</li> <li>Collect Adverse Events (AEs)</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>Urine dipstick/culture*</li> <li>NAAT for GC/CT*</li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>HIV-1 serology*</li> <li>Syphilis serology*</li> <li>Blood DPV levels (Target: At ~24 hours)</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>Trichomonas test*</li> <li>Wet prep &amp; vaginal pH*</li> <li>Herpes culture*</li> <li>Vaginal biomarkers</li> <li>Vaginal Gram stain</li> <li>CVF DPV levels (Target: At ~24 hours)</li> </ul>
	<b>Breast</b>	<ul style="list-style-type: none"> <li>Breast milk for DPV levels and lipids (Target: ~24 hours)</li> <li>Breast milk for anti-viral activity (Target: ~24 hours)</li> </ul>

\*if indicated

## 7.4.2 Visit 4- Day 7

Table 5: Visit 4- Day 7

<b>Visit 4- Day 7</b>		
<b>Component</b>	<b>Procedure/Analysis</b>	
<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/contact</li> </ul>	
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>• HIV pre- and post-test counseling*</li> <li>• Protocol adherence counseling (i.e., VR use instructions, counseling on collection/storage of breast milk at home, etc.)</li> <li>• Sexual practices assessment</li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical history</li> <li>• Review/update concomitant medications</li> <li>• Physical exam*</li> <li>• Breast exam*</li> <li>• Pelvic exam</li> <li>• Digital exam by clinician to check VR placement*</li> <li>• Collect from the participant the breast milk expression and product use (removals &amp; expulsions) log(s)</li> <li>• Treatment for reproductive tract infection (RTI)/urinary tract infection (UTI), STIs or mastitis*</li> <li>• Provision of contraception and contraception counseling*</li> <li>• Disclosure of available test results</li> <li>• Collect AEs</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Urine dipstick/culture*</li> <li>• NAAT for GC/CT*</li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• HIV-1 serology*</li> <li>• Syphilis serology*</li> <li>• Blood DPV levels</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>• Trichomonas test*</li> <li>• Wet prep &amp; vaginal pH*</li> <li>• Herpes culture*</li> <li>• Vaginal biomarkers</li> <li>• Vaginal Gram stain</li> <li>• CVF DPV levels</li> </ul>
	<b>Breast</b>	<ul style="list-style-type: none"> <li>• Retrieval of breast milk samples expressed at home</li> <li>• Breast milk for DPV levels and lipids</li> <li>• Breast milk for anti-viral activity</li> </ul>

\*if indicated

### 7.4.3 Visit 5- Day 14: Ring Removal

Table 6: Visit 5- Day 14: Ring Removal

Visit 5- Day 14: Ring Removal		
Component	Procedure/Analysis	
<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/contact</li> </ul>	
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>HIV pre- and post-test counseling*</li> <li>Protocol adherence counseling (i.e., counseling on collection/storage of breast milk at home, etc.)*</li> <li>Sexual practices assessment</li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>Review/update medical history</li> <li>Review/update concomitant medications</li> <li>Physical exam*</li> <li>Breast exam*</li> <li>Pelvic exam</li> <li>Collect from the participant the breast milk expression and product use (removals &amp; expulsions) log(s)</li> <li>Treatment for reproductive tract infection (RTI)/urinary tract infection (UTI), STIs or mastitis*</li> <li>Provision of contraception and contraception counseling*</li> <li>Disclosure of available test results</li> <li>Collect AEs</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>Urine dipstick/culture*</li> <li>NAAT for GC/CT*</li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>HIV-1 serology*</li> <li>Syphilis serology*</li> <li>Blood DPV levels (Target: At ring removal)</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>Trichomonas test*</li> <li>Wet prep &amp; vaginal pH*</li> <li>Herpes culture*</li> <li>Vaginal biomarkers</li> <li>Quantitative vaginal culture</li> <li>Vaginal Gram stain</li> <li>CVF DPV levels (Target: At ring removal)</li> </ul>
	<b>Breast</b>	<ul style="list-style-type: none"> <li>Breast milk for DPV levels and lipids (Target: At ring removal)</li> <li>Breast milk for anti-viral activity (Target: At ring removal)</li> <li>Retrieval of breast milk samples expressed at home</li> </ul>
<b>Study Product/Supplies</b>		<ul style="list-style-type: none"> <li>Removal and collection of study VR</li> </ul>

\*if indicated

## 7.4.4 Visit 6- Day 16: Study Exit/Termination Visit

Table 7: Visit 6- Day 16: Study Exit/Termination Visit

Visit 6- Day 16: Study Exit/Termination Visit		
Component	Procedure/Analysis	
<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/contact*</li> </ul>	
<b>Counseling</b>	<ul style="list-style-type: none"> <li>HIV pre- and post-test counseling and referral*</li> <li>Sexual practices assessment</li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>Review/update medical history</li> <li>Review/update concomitant medications</li> <li>Physical exam*</li> <li>Breast exam</li> <li>Pelvic exam</li> <li>Collect from the participant the breast milk expression and product use (removals &amp; expulsions) log(s)*</li> <li>Treatment for reproductive tract infection (RTI)/urinary tract infection (UTI), STIs or mastitis*</li> <li>Provision of contraception and contraception counseling*</li> <li>Disclosure of available test results</li> <li>Collect AEs</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>hCG</li> <li>Urine dipstick/culture*</li> <li>NAAT for GC/CT*</li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>HIV-1 serology*</li> <li>Syphilis serology*</li> <li>Blood DPV levels (Target: ~48 hours after ring removal)</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>Trichomonas test*</li> <li>Wet prep &amp; vaginal pH*</li> <li>Herpes culture*</li> <li>Vaginal biomarkers</li> <li>Quantitative vaginal culture</li> <li>Vaginal Gram stain</li> <li>CVF DPV levels (Target: ~48 hours after ring removal)</li> </ul>
	<b>Breast</b>	<ul style="list-style-type: none"> <li>Breast milk for DPV levels and lipids (Target: ~48 hours after ring removal)</li> <li>Breast milk for anti-viral activity (Target: ~48 hours after ring removal)</li> <li>Retrieval of breast milk samples expressed at home*</li> </ul>

\*if indicated

## 7.5 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. In the event that a clinic visit and/or study procedures are missed, an interim visit may be necessary. The SSP should be referenced for procedural guidance.



## **7.6 Follow-up Procedures for Participants Who Permanently Discontinue Study Product**

### **7.6.1 Participants Who Become Infected with HIV-1**

If a participant becomes infected with HIV-1 after the Enrollment Visit, she will be referred to local care and treatment services and may return to the research clinic for additional counseling and other support services, as needed. Continued study participation would be of no added benefit, thus follow-up visits will be discontinued and the participant will be considered terminated from the study. Participants who seroconvert after enrollment may be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), as clinically indicated per discussions between IoR and LC. Please reference the MTN-029/IPM 039 SSP Manual for additional details ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)).

### **7.6.2 Participants Who Become Pregnant**

If a participant becomes pregnant, she will be referred to local health care services and may return to the research clinic for additional counseling, as needed. Continued study participation would be of no added benefit to the participant, thus follow-up visits and procedures (other than ascertainment of pregnancy outcome) will be discontinued and the participant will be considered terminated from the study.

For additional details regarding obtaining pregnancy outcome, please reference the MTN-029/IPM 039 SSP ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)).

### **7.6.3 Participants Who Permanently Discontinue Study Product for Other Reasons**

Participants who permanently discontinue study product use for any reason (clinician-initiated or self-initiated) will be considered terminated from the study as continued study participation would be of no added benefit. Participants will, however, be asked to complete the procedures outlined in the Study Exit/Termination Visit (Section 7.4.4), if willing.

Participants who permanently discontinue study product use due to an AE must continue to be followed until resolution or stabilization of the AE is documented.

## **7.7 Study Product Use/Adherence Counseling**

Study staff will document proper insertion and placement of the VR. Product adherence counseling will be provided to study participants upon enrollment in the study and as needed. Counseling will be provided in accordance with the SSP and will include reminders to contact study staff with questions about study product use.

## 7.8 Pharmacokinetic and Pharmacodynamic Measures and Specimen Collection

For the purposes of scheduling subsequent evaluation and follow-up, the date of insertion of the vaginal ring will be considered Day 0, which is also the Enrollment Visit. The time of ring insertion will be considered Time 0. Pharmacokinetic and pharmacodynamic measures are timed by hours passed since ring insertion; see MTN-029/IPM 039 SSP for additional details.

**Table 8: PK Specimen Collection Schedule**

STUDY VISIT	PK and PD Specimen Collection
Visit 1: Screening	<ul style="list-style-type: none"> <li>• Breast milk for baseline</li> </ul>
Visit 2: Enrollment (Day 0)	<ul style="list-style-type: none"> <li>• Blood (Target: pre-insertion, hr 3 and hr 6)</li> <li>• CVF (Target: pre-insertion, hr 3 and hr 6)</li> <li>• Breast milk for DPV level and lipids (Target: pre-insertion, hr 3 and hr 6)</li> <li>• Breast milk for anti-viral activity (Target: pre-insertion, hr 3 and hr 6)</li> </ul>
Visit 3: Day 1	<ul style="list-style-type: none"> <li>• Blood (Target: 24 hours)</li> <li>• CVF (Target: 24 hours)</li> <li>• Breast milk for DPV level and lipids (Target: 24 hours)</li> <li>• Breast milk for anti-viral activity (Target: 24 hours)</li> </ul>
HOME COLLECTION (DAY 2-6)	<i>Participants are to ideally collect a minimum of 2 daily samples of breast milk- all samples may not be analyzed</i>
Visit 4: Day 7	<ul style="list-style-type: none"> <li>• Blood</li> <li>• CVF</li> <li>• Breast milk for DPV level and lipids</li> <li>• Breast milk for anti-viral activity</li> </ul>
HOME COLLECTION (DAY 8-13)	<i>Participants are to ideally collect a minimum of 2 daily samples of breast milk- all samples may not be analyzed</i>
Visit 5: Day 14	<ul style="list-style-type: none"> <li>• Blood (Target: At ring removal)</li> <li>• CVF (Target: At ring removal)</li> <li>• Breast milk for DPV level and lipids (Target: At ring removal)</li> <li>• Breast milk for anti-viral activity (Target: At ring removal)</li> </ul>
HOME COLLECTION (Day 15)	<i>Participants are to ideally collect a minimum of 2 samples of breast milk- all samples may not be analyzed</i>
Visit 6: Day 16	<ul style="list-style-type: none"> <li>• Blood (Target: 48 hours after ring removal)</li> <li>• CVF (Target: 48 hours after ring removal)</li> <li>• Breast milk for DPV level and lipids (Target: 48 hours after ring removal)</li> <li>• Breast milk for anti-viral activity (Target: 48 hours after ring removal)</li> </ul>

## 7.9 Clinical Evaluations and Procedures

### **Physical Examination**

The physical examination 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\*
- Oral mucosa\*
- Lymph nodes\*
- Neck\*
- Heart\*
- Lungs\*
- Extremities\*
- Skin\*
- Neurological\*
- Other components as indicated by participant symptoms

\*may be omitted after the Screening Visit

### **Pelvic Examination**

- Vulva
- Perianal area
- Speculum exam
- Bimanual exam
  - Cervix
  - Uterus
  - Adnexae

### **Breast Examination**

Breast exams will be conducted in the usual fashion including evaluation of the skin and the presence of any new masses and/or new clinically relevant findings.

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-029/IPM 039 SSP Manual.

## **7.10 Laboratory Evaluations**

### Local Laboratory

The local laboratory, site investigator, or designee will run the following maternal laboratory evaluations, as indicated per protocol:

- Urine pregnancy test
- Urine NAAT for chlamydia and gonorrhea
- AST/ALT
- HIV-1 serology
- Confirmatory testing for HIV
- Syphilis serology
- Cervicovaginal NAAT for GC/CT
- Trichomonas test
- Wet prep and vaginal pH
- Herpes

### Laboratory Center (LC)

LC will perform the following laboratory evaluations:

- Quantitative vaginal cultures
- Gram stains
- Vaginal biomarkers
- CVF DPV levels
- Blood DPV level- Pharmacology LC
- Breast milk for DPV levels and characterization of breast milk composition, including assays for total lipids - Pharmacology LC
- Breast milk for anti-viral activity

### IPM or MTN Designated Laboratory:

- Residual drug

## **7.11 Specimen Collection and Processing**

The study site will adhere to the standards of good clinical laboratory practice in accordance with current DAIDS Laboratory Requirements and the MTN-029/IPM 039 Study Specific Procedures Manual ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)) 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, the

site is permitted to re-draw specimens. Further, as part of quality control, researchers may need to look at short pieces of non-coding repetitive DNA sequence (3-7 base pairs) from blood in the event of sample mix-up. This test will only let researchers know the number of times this short segment is repeated and not specific genes or specific sequences of base pairs. This sequence element does not contain any information about genes, therefore researchers will not be able to identify if participants are predisposed to specific diseases or any other genetic information based on this information. This test will be an important tool for distinguishing whether two samples collected at the same or different time points are likely from the same person. The test will only be used as part of a sample investigation with the knowledge of the site in situations where a known or suspected sample mix-up has occurred. No genetic testing (limited or genome-wide) is planned on leftover samples that are stored for the purposes of future research.

### **7.12 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>)

### **7.13 Biohazard Containment**

As the acquisition 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/designees are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. A subgroup of the Protocol Team, including the Protocol Co-Chairs, DAIDS Medical Officer, Protocol Safety Physician(s), IPM Safety Physician(s), and SDMC Clinical Affairs Safety Associate will serve as the Protocol Safety Review Team (PSRT). The MTN SDMC prepares routine AE and clinical data reports 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, and the IPM safety physician 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 acquisition and medical ethics may be invited to join the PSRT safety review. A recommendation to pause 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.

The Study Monitoring Committee (SMC) will review participant safety data as part of their regular reviews (see Section 10.7.1), since no Data and Safety Monitoring Board oversight is planned for MTN-029/IPM 039. The 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 Site IoR will notify the responsible IRB expeditiously.

In addition to the safety monitoring done by the PSRT, the MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, and study or lab issues. These reviews will take place 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.

### **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. AE collection is initiated upon insertion of the study product at the Enrollment Visit. The term “investigational product” for this study refers to the dapivirine vaginal ring.

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 on CRFs all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. AE severity and laboratory tests will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, November 2014 and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, November 2007). Please note that asymptomatic BV and asymptomatic candidiasis will not be reportable AEs. In addition, fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses are reported

as reproductive system AEs. Further, changes in genital bleeding judged to be related to a woman's contraceptive use or return of menstruation postpartum will not be considered an AE, nor will a pelvic exam be required for follow-up. Bleeding at the time of speculum insertion or cervicovaginal specimen collection that is judged by the clinician to be within the range of normally anticipated bleeding for that procedure will not be reportable as an AE. Bleeding of greater quantity or longer duration than typical will still be reported. 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 AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For each study participant, expedited AE reporting will be undertaken throughout the scheduled duration of follow-up, i.e., from the time of enrollment through study exit/termination.



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 agent for which expedited reporting is required is the dapivirine VR
- For all SAEs submitted, sites must file an initial report and an update to IPM and the DAIDS Medical Officer with the final or stable outcome unless the initial SAE submitted had a final or stable outcome noted already

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

The grading of severity of events and the reporting period will be the same as for all AEs, as described in Section 8.3.1. The most current Division of AIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, November 2014 and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, November 2007), will be used and is available on the RSC website at [http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS\\_AE\\_GRADING\\_TABLE\\_v2\\_NOV2014.pdf](http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf).

#### **8.4.4 Expedited AE Reporting Period**

The expedited AE reporting period for this study begins once the participant is enrolled and continues up through the participant's final study visit (Study Exit/Termination Visit).

After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

#### **8.5 Pregnancy and Pregnancy Outcomes**

Pregnant women are excluded from this study.

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. The site IoR/designee will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. Site IoR/designees also will submit AE information and any other relevant safety information to their ECs/IRBs in accordance with EC/IRB requirements.

## **8.7 Social Harms Reporting**

Although study sites will 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. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the PSRT and responsible site ECs/IRBs according to their individual requirements. In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Each site will provide such care and counseling in accordance with standardized guidance provided in the MTN-029/IPM 039 SSP Manual. While maintaining participant confidentiality, study sites may engage their community advisory boards (CABs) in exploring the social context surrounding instances of social harm.

# **9 CLINICAL MANAGEMENT**

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

## **9.1 Grading System**

AE severity grading is described in Section 8.4.3.

## **9.2 Dose Modification Instructions**

No dose modifications will be undertaken in this study.

## **9.3 General Criteria for Permanent Discontinuation of Study Product**

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

- After enrolling in the study, provides breast milk to child(ren) or anyone else, for immediate consumption, banking, or freezing, or expresses an intention to do so
- Acquisition of HIV infection; for those who acquire HIV, study product should be held beginning immediately upon recognition of the first reactive rapid HIV test
- Pregnancy
- Continued use of the vaginal ring would be harmful
- 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.

## **9.4 Follow-up in Response to Observed 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 2.0, November 2014 and/or the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, November 2007) not specifically addressed below, regardless of relatedness to study product, may continue product use.

### **Grade 3 Unrelated**

Participants who develop a Grade 3 AE as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, November 2014 and/or the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, November 2007) that is not specifically addressed below and is judged by the IoR/designee to be not related to study product may continue product use.

### **Grade 3 Related and Grade 4 and Higher**

For participants who develop a Grade 3 related or any Grade 4 or higher AE as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, November 2014 and/or the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, November 2007) regardless of relationship to study product, study product must be permanently discontinued.

## 9.5 Other Clinical Events

### **STI/RTI**

The IoR/designee should manage STI/RTI per current US Centers for Disease Control Guidelines. Observed single dose treatment should be provided whenever possible, per clinician discretion. When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible. Study VR need not be discontinued in the event of an STI/RTI requiring treatment, unless permanent discontinuation guidelines apply or the IoR exercises their discretion.

### **Genital Complaints**

A thorough evaluation of genital complaints is expected in the context of this study. Observed single dose treatment should be provided whenever possible, per clinician discretion. When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible. Study VR need not be discontinued in the event of genital complaints, unless permanent discontinuation guidelines apply or the IoR exercises their discretion.

### **Suspected Complication of Lactation**

Participants judged by the IoR/designee to have a suspected complication of lactation or weaning (e.g., mastitis, lactation suppression, etc.) will be referred to appropriate clinical management in a timely fashion. Treatment for mastitis and other complications may be undertaken at the study site, at the discretion of the IoR/designee. Every effort will be made to facilitate the participant's access to appropriate clinical management. Study VR need not be discontinued in the event of lactation complications, however the PSRT must be consulted.

If a suspected finding is reported by a participant between scheduled visits, an interim visits may be scheduled at the discretion of the site investigator.

Should the IoR/designee determine that a permanent discontinuation is warranted for any of the *Other Clinical Events* mentioned above or for any other reason, consultation with the PSRT is required.

## 9.6 HIV-1 Infection

A participant who has a positive test for HIV must have study product permanently discontinued and will be terminated, as per Section 7.6.1.

## 9.7 Pregnancy

Pregnancy testing will be performed 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 becomes pregnant during the course of the study will have study product discontinued and will be terminated from the study, as per Section 7.6.2. Participants 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.

### **9.8 Participants who State an Intention to Reinitiate Feeding Infants with their Own Breast Milk after Study Product Exposure**

Only participants who have weaned their child (or children) will be enrolled. Study staff will follow current CDC guidelines in their approach to answering questions from potential participants regarding breastfeeding, including a discussion of the known benefits of breastfeeding.<sup>21</sup>

However, it is possible that some women will enroll in the study, be exposed to study product, and then wish to resume feeding their infant(s) with their own milk. In this case, participants will be permanently discontinued from study product, and counseled on a case-by-case basis regarding the discarding of expressed milk and resumption of infant feeding with own breast milk. Study staff will also counsel participants regarding the possibility of dapivirine exposure and the unknown risks of such an exposure.

### **9.9 Criteria for Early Termination of Study Participation**

Participants may voluntarily withdraw from the study for any reason at any time. The IoR/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 IPM, MTN, and NIAID or other 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.

## **10 STATISTICAL CONSIDERATIONS**

### **10.1 Overview and Summary of Design**

This is a Phase 1 open-label, single-arm pharmacokinetic study of dapivirine 25 mg VR worn continuously for 14 days in HIV-uninfected lactating women. Sixteen lactating women will be enrolled, and the active study VR will be administered at the study site on Day 0 and removed on Day 14.

## 10.2 Study Endpoints

Consistent with the primary study objectives to assess the pharmacokinetics of the dapivirine VR worn continuously for 14 days, the following endpoints will be assessed:

- Blood dapivirine levels
- Breast milk dapivirine levels
- Cervicovaginal fluid dapivirine levels

Consistent with the secondary study objective to assess safety and tolerability of dapivirine VR worn continuously for 14 days, the secondary safety endpoints are the proportion of women with the following:

- Evidence of a Grade 2 or higher genitourinary adverse event as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014 and/or Addenda 1 and 3 (Female Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies).
- Evidence of a Grade 3 or higher adverse event as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014

Consistent with the secondary study objective to assess adherence to the dapivirine VR worn continuously for 14 days, the following secondary adherence endpoint will be assessed:

- Blood dapivirine levels and residual levels in returned VRs

## 10.3 Primary Study Hypotheses

We hypothesize the following:

- Dapivirine will be detectable at low levels in breast milk, and only in a minority of participants
- Blood dapivirine levels will be detectable at low levels in all women
- Continuous exposure via use of the dapivirine VR by lactating women for 14 days will be well-tolerated and not associated with significant toxicity in women.

## 10.4 Sample Size and Power Calculations

For the proposed study sample size, the statistical properties of this study in assessing the PK and safety of dapivirine VR are summarized below. An event is defined as a participant either having a detectable level of dapivirine or having at least one safety endpoint. With approximately 16 participants being administered the dapivirine VR, the probabilities of observing various numbers of events are listed in the following table,

assuming various true event rates. For instance, if the true rate is 5%, the probability of observing that endpoint in at least one participant out of 16 participants is 0.560. A higher true event rate will result in a larger probability to observe at least one event. So if the true rate is 10%, the probability of observing that endpoint in at least one participant out of 16 participants is 0.815.

**Table 9: The Probability of Observing a Number of Participants of Having an Event Given the True Event Rate for a Sample Size of 16**

Event Rate	P (0 events   n=16)	P (≥1 event   n=16)	P (≥2 events   n=16)
1%	0.851	0.149	0.011
5%	0.440	0.560	0.189
10%	0.185	0.815	0.485
15%	0.074	0.926	0.716
25%	0.010	0.990	0.937
35%	0.001	0.999	0.990

If the overall event rate was expected to be 25%, 16 women provide 80% power to exclude event rates > 57.3% (62.5% with 90% power). For endpoints where no or very low event rates are expected (e.g., dapivirine in breast milk), 16 women would provide 80% power to exclude an event rate > 31.8% assuming the true rate is 6.25% (Table 10).

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 16 participants receiving dapivirine VR experience a detectable PK event, the 95% exact 2-sided upper confidence bound for the true rate of such events is 20.6%.

**Table 10: Exact 2-sided 95% Confidence Intervals Based on Observing a Particular Event Rate and Event Rates That May Be Excluded with 80% and 90% Power Given the True Event Rate for a Sample Size of 16**

Event rate	Number of events observed for N=16	Exact 95% confidence interval (%)	80% power to exclude an event rate greater than:	90% power to exclude an event rate greater than:
0%	0	0.0, 20.6	9.6%	13.4%
6.25%	1	0.2, 30.2	31.8%	37.1%
12.50%	2	1.6, 38.4	38.5%	43.9%
18.75%	3	4.1, 45.7	51.2%	56.6%
25.00%	4	7.3, 52.4	57.3%	62.5%
31.25%	5	11.0, 58.7	63.2%	68.2%
37.50%	6	15.2, 64.6	69.0%	73.7%
43.75%	7	19.8, 70.1	74.6%	79.0%
50.00%	8	24.7, 75.4	80.1%	84.0%

Additional participants may enroll in the study, at the discretion of the protocol team, to replace currently enrolled participants who are non-adherent to the study product and/or the study visit schedule. Thus, in the event that additional participants are recruited for this purpose, the total sample size at the end of the study may slightly exceed 16 participants who received the dapivirine VR.

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

The accrual period will be 12-18 months. The study sites will recruit and enroll a total of 16 participants. Each participant will be followed for 16 days following VR administration. Once a participant has enrolled in the study, the study site will make every reasonable effort to retain her for the entire study period.

## **10.6 Blinding**

This is an open-label and unblinded trial.

## **10.7 Data and Safety Monitoring and Analysis**

### **10.7.1 Study Monitoring Committee (SMC)**

In addition to the safety monitoring done by the PSRT (described in Section 8), the MTN SMC will be responsible for study oversight by conducting interim reviews of study progress, including rates of participant accrual, participant retention, protocol and intervention adherence, data quality, laboratory quality and completion of primary and secondary endpoint assessments. Please reference the MTN-029/IPM 039 SSP Manual for additional details ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)). Since MTN-029/IPM 039 is not subject to DSMB review, the SMC also will review participant safety data, as specified in the MTN Manual of Procedures. These reviews will take place approximately every 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. The SMC may consider recommending termination of this study if recruitment is lower than targeted, or if study data quality is poor. If at any time, a decision is made to discontinue participants, IPM, after consultation with the protocol team, will inform the US Food and Drug Administration (FDA). The Site PIs will notify the responsible IRBs expeditiously.

## **10.8 Primary Analysis**

Descriptive statistics to assess participant characteristics 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). Similarly, descriptive statistics for continuous variables will be used to describe levels of dapivirine in blood, in breast milk, and in cervicovaginal fluid. If a substantial number of women are below the limit of detection of the assay, descriptive statistics for continuous variables



will not be used. Rather, proportion of women with detectable levels will be computed along with an exact 95% confidence interval based on the Clopper-Pearson method.

Blood plasma pharmacokinetics of dapivirine will be evaluated after VR administration. Samples to measure drug concentration will be taken at multiple time points throughout the study period according to Table 8: PK Specimen Collection Schedule in Section 7 above. Pharmacokinetic parameter estimates will include peak concentration ( $C_{max}$ ), time to peak concentration ( $T_{max}$ ), and area under the concentration time curve (AUC) for dapivirine in the blood. Descriptive statistics will be used to summarize these PK parameters in the cohort. Breast milk and cervicovaginal fluid dapivirine levels will also be summarized using descriptive statistics. The ratio of concentrations of dapivirine in blood relative to temporally matched breast milk and cervicovaginal fluid concentrations will be calculated and summarized using descriptive statistics.

## 10.9 Secondary Analyses

### Safety Endpoints

All visits in which a woman has been exposed to the study product will be included in the secondary analyses of safety. To assess genitourinary safety, the number and the percentages of participants experiencing such a safety endpoint (see Section 10.2) will be tabulated. Each participant will contribute once in each category (i.e., only for the highest severity AE for each participant) for the calculation of event rates. Exact binomial confidence intervals will be calculated for each safety endpoint.

### Adherence

To assess adherence of women to the dapivirine VR, descriptive statistics will be used to describe the levels of dapivirine in blood and the proportion of participants with detectable dapivirine in blood. Also, the amount (mg) of dapivirine remaining in the used VR removed on Day 14 will be calculated and compared to the initial dose of 25 mg to determine how much dapivirine was released over the 14 days of product use. In adherent participants, this amount is expected to be low, and below 4 mg released (the amount released on average over 28 days of use in prior studies).

## 10.10 Missing Data

We are targeting a retention rate of 95% over the 16 day study period. Based on previous MTN trials, we expect to have minimal missing data. If participants are non-adherent to the study product or the visit schedule, they may be replaced, as mentioned above. If missing data rates are higher than anticipated (over 15%) for individual pharmacokinetic measure time points, then additional participants may enroll in the study, at the discretion of the protocol team, to replace currently enrolled participants.

# 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. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study site for verification and resolution. As part of the study activation process, the 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.

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

The study site 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

The study site 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
- Verify that current license/certification is available on site for study staff listed on the current FDA Form 1572, DAIDS IoRs, and Delegation of Responsibilities Log/Form.

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 certain study procedures. The IoR/designee will also allow inspection of all study-related documentation by authorized representatives of the MTN LOC, SDMC, and LC; NIAID, FDA, IPM, OHRP and local and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

## **13 HUMAN SUBJECTS PROTECTIONS**

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR/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 LOC, 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 site. Any amendments to the protocol must be approved by DAIDS and 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. The study site 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, the 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, the site 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, the site should implement the amendment immediately. The site is 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 of the required documents have been received. Site-specific ICF(s) *will not* be reviewed and approved by the DAIDS PRO and the site will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

### **13.3 Study Coordination**

IPM holds the Investigational New Drug (IND) application for this study. Copies of all regulatory documents submitted to this IND by IPM will be forwarded to DAIDS for cross-referencing with other INDs for the study product. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement executed by NIAID and IPM.

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; clinical management of AEs; dispensing study product and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN LOC, SDMC, LC 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

It is not expected that this trial will expose human subjects to unreasonable risk.

Pelvic examination and procedures may cause mild discomfort and/or vaginal bleeding or spotting. Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. 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. It is possible that the participant and her partner may feel the ring during sexual activity.

Participants also could experience problems associated with use of study product in their partner relationships.

Use of the study VR may lead to vaginal symptoms, including irritation, increased discharge, and discomfort (including with vaginal intercourse). It is possible that a participant may have an allergic reaction to the study product. Symptoms of an allergic reaction include rash or other skin irritation, itching, joint pain, or difficulty in breathing.

Based on AEs reported among female participants in previous studies, dapivirine VRs may be associated with the following:

- Metrorrhagia
- Vaginal discharge
- Vaginal candidiasis
- Vaginitis bacterial
- Urinary tract infection

Based on *in vitro* data, HIV-infected participants who have prolonged exposure to low concentrations of dapivirine by continuing to use the ring after infection may have a risk of selecting viruses carrying NNRTI resistance-associated mutations. Clinical relevance has yet to be established.

Some women experience discomfort the first few times they pump, but pumping should not be painful, result in sore or irritated nipples, or cause bleeding. These may be signs of an injury, problems with the breast pump, or errors in pumping technique.

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

#### **13.4.2 Benefits**

Participation in this study likely will have no direct benefit to participants, yet the participant may appreciate the opportunity to contribute to the body of knowledge in the field of microbicide and HIV prevention research. Specifically, information learned in this study may help to understand issues important for broader implementation of the dapivirine ring and/or for the development of other safe and effective interventions to prevent HIV acquisition.

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical examination, breast examination, pelvic examination, and routine laboratory testing. Participants will be provided STI treatment in accordance with US CDC guidelines. In addition, STI testing, counseling and treatment, as well as HIV testing and counseling

will be available for participants' partners. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals.

### **13.5 Informed Consent Process**

Each study participant will provide written informed consent prior to screening. Written informed consent will also be obtained for long-term specimen storage and possible future testing. 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 will specifically address the following topics of importance to this 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 distinction between research and clinical care
- The right to withdraw from the study at any time
- New information about the study product and information about other effective HIV-prevention products will be provided to MTN-029/IPM 039 participants as they become available.

## **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, 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 securely. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' identification numbers to identifying information will be stored in a 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, including study monitors
- PPD
- Study staff
- Site IRBs/ECs

The MTN has a Certificate of Confidentiality from the US Department of Health and Human Services that is applicable to 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. Women who test positive for pregnancy after Enrollment will have study product discontinued and will be terminated from the study Section 7.6.2. A urine pregnancy test will be performed at scheduled study visits, and additionally at interim visits as indicated; the IoR/designee will permanently discontinue study product for participants who test positive for pregnancy. During the informed consent process, women will be informed that the VR is not a method of contraception and the effects of the VR on a developing human fetus are unknown. No adequate and



well-controlled studies in pregnant women have been completed to support their inclusion to date.

### **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/adolescents 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. Each study site will determine appropriate compensation with their overseeing IRB.

### **13.9 Communicable Disease Reporting**

Study staff will comply with local requirements to report communicable infections 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. 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**

An individual who has been identified as infected with HIV-1 will be managed or referred for management according to the local standard of care. Should a participant test positive for HIV after Visit 2, follow-up procedures will be performed as per Section 7.6.1. Please refer to Section 9.6 for additional details.

### **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 NIAID and IPM 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

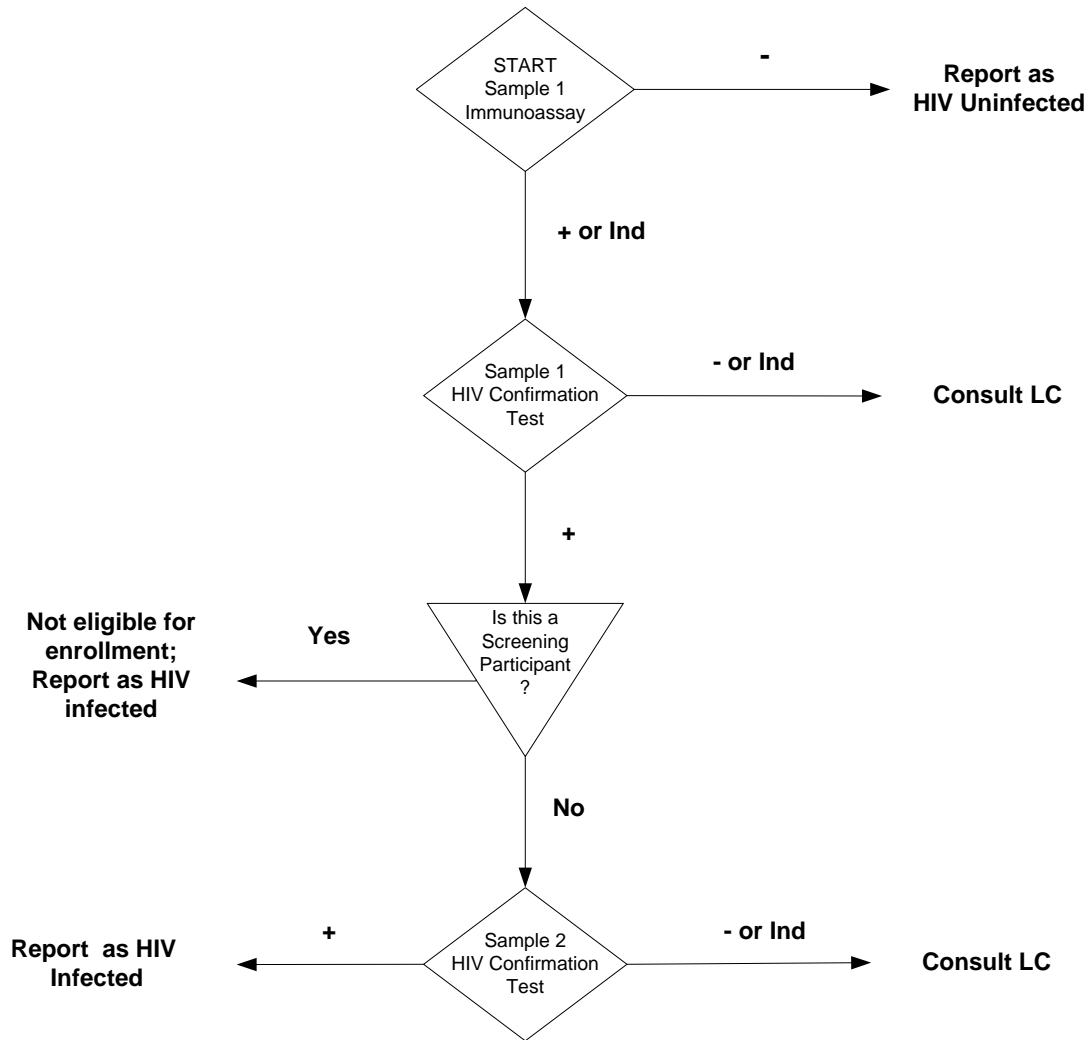
## APPENDIX I: SCHEDULE OF STUDY VISITS AND PROCEDURES

		Visit 1 SCR	Visit 2 ENR (Day 0)	Visit 3 (Day 1)	Visit 4 (Day 7)	Visit 5 (Day 14)	Visit 6 (Day 16)
<b>ADMINISTRATIVE AND REGULATORY</b>							
Obtain Informed consent(s)		X					
Assign a unique Participant Identification (PTID) number		X					
Assess and/or confirm eligibility		X	X				
Demographic information		X					
Collect/review/update locator information		X	X	X	X	X	X
Provide Reimbursement		X	X	X	X	X	X
Schedule next visit/contact		*	*	X	X	X	*
<b>BEHAVIORAL</b>							
HIV pre- and post-test counseling and referral for repeat testing if indicated		X	μ	*	*	*	*
Counseling on breast milk production maintenance		*					
Protocol adherence counseling (i.e., VR use instructions, counseling on collection/storage of breast milk at home, etc.)			X	X	X	*	
Sexual practices assessment			X	X	X	X	X
<b>CLINICAL</b>							
Medical eligibility information (including exclusionary medical conditions and medications)		X	X				
Medical history		X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X
Physical exam		X	X	*	*	*	*
Breast exam		X	X	*	*	*	X
Pelvic exam		X	X	X	X	X	X
Digital exam by clinician to check VR placement			X	*	*		
Collect from the participant the breast milk expression and product use (removals & expulsions) log(s)					X	X	*
Treatment for reproductive tract infection (RTI)/urinary tract infection (UTI), STIs or mastitis		*	*	*	*	*	*
Provision of contraception and contraception counseling		*	*	*	*	*	*
Disclosure of available test results		X	X	X	X	X	X
Collect AEs				X	X	X	X
<b>LABORATORY</b>							
URINE	hCG	X	X				X
	Urine dipstick/culture	*	*	*	*	*	*
	NAAT for GC/CT		*	*	*	*	*
BLOOD	HIV-1 serology	X	μ	*	*	*	*
	Plasma archive		X				
	AST/ALT	X					
	Syphilis serology	▲	*	*	*	*	*
	Blood DPV levels		X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>
PELVIC	Cervical NAAT for GC/CT	X					
	Trichomonas test	X	*	*	*	*	*

		Visit 1 SCR	Visit 2 ENR (Day 0)	Visit 3 (Day 1)	Visit 4 (Day 7)	Visit 5 (Day 14)	Visit 6 (Day 16)
	Pap smear interpretation	^	^				
	Wet prep & vaginal pH	*	*	*	*	*	*
	Herpes culture	*	*	*	*	*	*
	Vaginal biomarkers		X	X	X	X	X
	Quantitative vaginal culture		X			X	X
	Vaginal Gram stain		X	X	X	X	X
	CVF DPV levels		X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>
BREAST	Breast milk sample for eligibility	X	X				
	Breast milk for anti-viral activity		X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>
	Breast milk for DPV levels and lipids		X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>	X <sup>∞</sup>
	Retrieval of breast milk samples expressed at home				X	X	*
<b>STUDY PRODUCT / SUPPLIES</b>							
Provision of study VR			X				
Insertion of one study VR and VR use instructions			X				
Removal and collection of study VR						X	
Supplies for breast milk collection			X				

X= required, \*= if indicated and/or per local standard of care, X<sup>∞</sup>=See Table 8 for additional details on sample collection, ▲= required if not completed (and documented) within the past year, μ= May be omitted if < 30 days has passed between the Screening and Enrollment Visit, ^= if indicated (if participant [over age 21] is unable to provide documentation of a satisfactory Pap smear within 3 years prior to enrollment)

## APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING



Ind: Indeterminate test results  
LC: Laboratory Center

**APPENDIX III: SAMPLE INFORMED CONSENT FORM (SCREENING,  
ENROLLMENT, LONG-TERM STORAGE AND FUTURE TESTING)**

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

**MTN-029/ IPM 039**

**Phase 1 Pharmacokinetic Study of the Dapivirine Vaginal Ring in Lactating  
Women**

**Version 1.0**

**June 30, 2015**

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

**PHONE: [Site to insert]**

**Short Title for the Study: Phase 1 PK Study of the Dapivirine Vaginal Ring in  
Lactating Women**

**INFORMED CONSENT**

You are being asked to take part in this research study because you are healthy, HIV-negative, 18 years or older, at least 6 weeks postpartum, and you are able to produce and express milk (lactating) but you have decided to stop breastfeeding. Approximately 16 lactating women will participate at two study sites in the United States. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). The study product in this clinical trial is a vaginal ring containing an anti-HIV medication, dapivirine. A vaginal ring is a flexible plastic ring that is inserted into your vagina. You will be asked not to remove the ring for approximately 14 continuous days. The dapivirine vaginal ring being tested in this study is **not** a birth control method. The study product is supplied by the International Partnership for Microbicides (IPM). At this site, the person in charge of this study is **[INSERT NAME OF PRINCIPAL INVESTIGATOR]**.

Before you decide if you want to join this study, we want you to learn more about it. This consent form gives you information about the study. Study staff will talk with you and answer any questions you may have. Once you read and understand the study and its requirements, you can decide if you want to join. If you do decide to take part in the trial, you will sign your name on this form. A copy of this document will be offered to you. Signing this consent form does not mean you will be able to join the study. You must first complete the screening tests and exams to see if you are eligible.

It is important to know that your participation in this research is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

Before you decide if you would like to participate in this research study, you should know that the American Association of Pediatrics (AAP) recommends that babies be exclusively breastfed for about the first 6 months of life. This means that your baby needs no additional foods (except Vitamin D) or fluids, unless medically indicated. Babies should continue to breastfeed for a year, and for as long as is mutually desired by the mother and baby. As long as breastfeeding is the right choice for you and your baby and supported by your health care provider you should continue to do so. If you decide to enroll in this study, you must agree to not provide breast milk to your child(ren) or anyone else, such as for immediate consumption, banking, or freezing.

### **WHAT IS THE PURPOSE OF THIS STUDY?**

The main purpose of this research study is to find out how the study drug, dapivirine, enters and exits the body, including whether and how it exits through breast milk, when the ring is inserted into the vagina for approximately 14 continuous days. Another purpose of this study is to find out if the ring is safe and well-tolerated. . This study will provide important information on the dapivirine vaginal ring when it is used by lactating women.

### **STUDY PRODUCT**

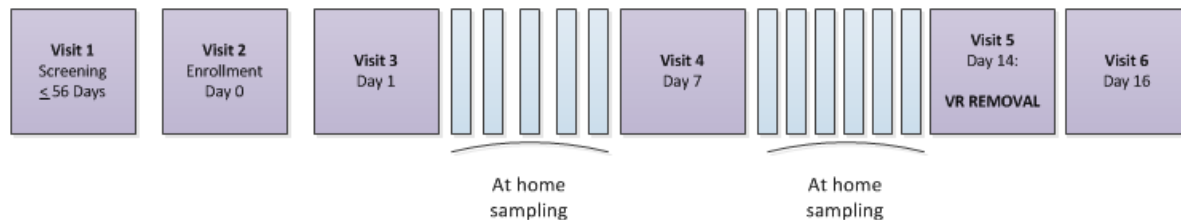
Dapivirine vaginal rings have been previously tested and found to be generally safe and well-tolerated. Dapivirine is currently being tested in other studies to see whether it can help to prevent the spread of HIV. HIV is the virus that causes AIDS. Dapivirine works by preventing HIV from making copies of itself, thereby stopping the spread of HIV in the body. Researchers do not yet know if the drug will work in humans to protect against HIV infection. There are only two known effective ways to prevent sexually transmitted HIV in women: condoms use during sex and/or the use of pre-exposure prophylaxis (PrEP). PrEP is a new HIV prevention method where people who do not have HIV take an oral tablet to reduce their risk of becoming infected. Study staff can provide you with additional information about PrEP if you are interested in learning more.

While dapivirine has been tested before in humans, this is the first time dapivirine has been studied in lactating women. Researchers would like to know if this drug is safe for use by breastfeeding women. To do this, they first need to better understand what effect these drugs have on the body, including the effect on breast milk and the vagina.

All participants will receive a vaginal ring containing dapivirine.



## WHAT WILL HAPPEN DURING THE MTN-029/ IPM 039 STUDY VISITS?



### Screening Procedures:

The MTN-029/IPM 039 study includes a total of 6 clinic visits, including the Screening Visit, which is taking place today if you decide to sign this informed consent form. Visits will take place here, at this study clinic.

### Screening Visit

The procedures done today 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), childbearing and lactation history, and your understanding of the study requirements. They may also ask to view your medical records, with your permission.
- You will be asked to provide and/or update study staff with your contact information (i.e., about how we can contact you).
- Study staff will:
  - Perform a physical exam and a breast exam.
  - Perform a pelvic examination:
    - The study clinician will use a speculum, a plastic or metal instrument used to separate the walls of the vagina, to check your vagina and cervix (the tissue that attaches the vagina to the uterus) for signs of infection, and other problems. They will also take some fluid from your vagina with a swab. These swabs will be used to test for sexually transmitted infections and diseases (commonly known as STIs or STDs) and other problems.
    - If you are over the age of 21 it may be necessary for you to have a Pap smear if you do not have results with you today of a Pap smear that was done in the past 3 years (a Pap smear is a test for cervical cancer). If your Pap result is not normal, you might not be able to be in the study; the study staff can discuss this with you.
  - Talk with you about the requirements of the study, including the importance of completing clinic visits, and study activities and procedures according to the study schedule.
  - Talk with you about any questions or concerns you have about the benefits and risks associated with breastfeeding and pumping.

- If you are still breastfeeding or pumping, study staff will talk with you about your questions and concerns about weaning, and your thoughts about when might be the right time to wean.
- If you have already weaned, you will be counseled regarding how to maintain your breast milk production while participating in this study.

At your Screening Visit, study staff will also:

- Test your urine for pregnancy
  - If you are pregnant you cannot join this study.
  - Study staff will talk with you about ways to avoid becoming pregnant
  - If you become pregnant at any time during the study, study staff will refer you to available medical care and other services you may need. The study does not pay for this care. You will not receive (or will stop using) the study vaginal ring and you will exit the study. The outcome of your pregnancy is important to study staff; therefore your pregnancy will be followed until the results of your pregnancy are known. We may contact you to find out about the health of your pregnancy. We may also contact you about a study that collects information about pregnancy and babies up to one year old.
- You will answer questions to confirm that you are able to join the study including whether you are using an effective method of contraception and intending to use that method for the entire time that you are in this study.
- If needed, staff will provide you with an acceptable method of contraception for use during your participation in the study. Acceptable contraceptive methods in this study include:
  - Hormonal methods (except for contraceptive vaginal rings)
  - Intrauterine devices (IUDs) inserted at least 28 days prior to enrollment
  - You engage in sex exclusively with women
  - Sterilization: You or your partner has been sterilized
  - Abstinence: You have been sexually abstinent for the past 90 days AND intend to remain abstinent during your participation in the study.
- Provide a breast milk sample to confirm that you are eligible for this study. If you are found to be eligible for this study this breast milk might be used for research purposes. If you are found not to be eligible for this study your sample will be destroyed.
- Take a blood sample **[SITES TO INSERT AMOUNT]**:
  - To test the health of your liver.
  - To test for infections that typically are passed through sex, including HIV

- You will be told your test results as soon as they are available. You will talk with the study staff about the meaning of your results, how you feel about them, and learn about 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 are sure of your status. To participate in the study you must receive the results of your HIV test. 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. The study staff will tell you about other studies you may be eligible for, if any.
- If needed, give you treatment or refer you for treatment of:
  - Sexually transmitted or other urinary or reproductive tract infections
  - Mastitis (inflammation or infection of mammary glands in the breast)
- Inform you about other services, if needed.
- Provide you with the results of your tests, when available. It is expected that all of your results will be available by **[SITES TO SPECIFY TIMEFRAME]**.
- Reimburse you for your visit
- Schedule your next visit to enroll in the study, if you are willing and eligible.

If you decide not to join MTN-029/IPM 039, blood and other samples collected at this visit will not be kept or used for any tests other than those listed above.

### **Enrollment Visit:**

Your Enrollment Visit (the visit where you join the study), will take about **[SITES TO INSERT TIME]**. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of mastitis or a urinary, genital, or other infection and/or other issues).

The following procedures are specific to the Enrollment Visit, which will take place up to 8 weeks after your Screening Visit. You will:

- Answer questions to confirm you are able to join the study
- Update study staff with your contact information (i.e., about where you live and how we can contact you)
- Talk with study staff about the following:
  - The rules of the study and how to follow the rules, including restrictions on sexual practices. **If you do not think you can abstain from sex for the 24 hours preceding each clinic visit then you should not join this study.**

Sex for this study is defined as penile-vaginal intercourse, anal intercourse, receptive oral intercourse, finger stimulation, and/or the use of sex toys.

*You will be asked to abstain from the following activities for the stated length of time highlighted below:*

<u>Activity:</u>	<u>Abstain For How Long?</u>
<ul style="list-style-type: none"> <li>• Anal intercourse</li> <li>• Penile-vaginal intercourse</li> <li>• Receptive oral intercourse</li> <li>• Tampon use</li> <li>• Inserting any objects into your vagina, including:               <ul style="list-style-type: none"> <li>○ Sex toys</li> <li>○ Female condoms</li> <li>○ Diaphragms</li> <li>○ Menstrual cups</li> <li>○ Cervical caps or any other vaginal barrier method</li> <li>○ Etc.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• For 24 hours prior to each clinic visit</li> </ul>
<ul style="list-style-type: none"> <li>• Vaginal products, including:               <ul style="list-style-type: none"> <li>○ Spermicides</li> <li>○ Lubricants</li> <li>○ Contraceptive VRs</li> <li>○ Douches</li> <li>○ Vaginal medications</li> <li>○ Etc.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• For the duration of study participation</li> </ul>

- You will be asked questions to confirm you are eligible and also be asked to express breast milk to confirm you are able to take part in this study. If you are found to be eligible, some of this breast milk may be used for research purposes.
- You will be asked about your sexual practices.
- You will also talk with study staff about sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex.
- Discuss any health or medical problems you may have had in the past or are currently experiencing or have occurred since your last visit (including what medications you are taking)
- Study staff will take blood samples [SITES TO INSERT AMOUNT] before you receive the study vaginal ring, and three and six hours later. An intravenous cannula (IV tube) may be placed for up to 6 hours after you receive the study

vaginal ring for the blood draws. These blood samples are collected for research purposes, including to learn how dapivirine enters and exits the body over time. We also will collect blood in case there is a question about your lab results in the future.

At the Enrollment Visit, you will also:

- Have a physical exam and a breast exam
- Have your urine tested for pregnancy
- Have your blood tested for HIV if more than 30 days have passed since your Screening Visit
- Have a pelvic exam
  - The study clinician will use a speculum.
  - The clinician may also collect samples from your cervix for a Pap smear if you do not have results with you today of a Pap smear that was done in the past 3 years (a Pap smear is a test for cervical cancer). If your Pap result is not normal, you might not be able to be in the study; the study staff can discuss this with you.
- You or the clinician will take some fluid from your vagina with a swab. These samples will be collected before you receive the study vaginal ring, and three and six hours later. The cervicovaginal fluid samples will be used for research purposes, including to measure how much dapivirine is present, test how the fluids protect against HIV in the laboratory, and other tests for research purposes. When these samples are collected at future visits similar tests will be done.
- Receive the study vaginal ring. The study clinician will insert the ring and perform an exam to ensure it is inserted correctly. You will be asked to keep the vaginal ring in place and not remove it between visits. Study staff will show you how to take the ring out in case you need to do so. You will also receive a study product use log, in which you will be asked to track any problems you may have while using the study product, such as the ring falling out or being removed. Study staff will talk with you about what to do if you have any problems or symptoms while using the ring.
- Study staff will talk with you if you encounter any problems or symptoms while undergoing the procedures at today's clinic visit
- Express breast milk samples before you receive the study vaginal ring, and 3 and 6 hours later. The milk collected will be used for research purposes only, to better understand how dapivirine enters and exits the body over time. These samples may also be tested for antiviral activity. When these samples are collected at future visits similar tests will be done.
- Talk with study staff about how to correctly collect and store samples of your breast milk at home in between clinic visits. Staff will also speak with you about whether you have access to a refrigerator with enough space to store your samples.

- Talk with study staff about what to do if you have any problems or symptoms while expressing breast milk, whether at the clinic or at home
- Receive supplies you will use to collect samples of your breast milk at home, including a breast pump (if you need it) and plastic bags. (The breast pump is yours to keep after your participation in the study).
- Receive treatment or be referred for treatment issues that the study staff may find
- Receive test results, if available
- Talk with study staff about any of your questions
- Be reimbursed for your visit
- Schedule your next visit, if applicable

### Visit 3:

Visit 3 will take place approximately 24 hours after your Enrollment Visit, and will take between **[SITES TO SPECIFY TIMEFRAME]** to complete. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of mastitis or a urinary, genital, or other infection and/or other issues).

At Visit 3, you will:

- Update study staff with your contact information
- Discuss any health or medical problems you may have had in the past or are currently experiencing or have occurred since your last visit (including what medications you are taking)
- Be asked about your sexual practices
- Talk with study staff about any problems that you may be experiencing as a result of wearing the vaginal ring or procedures performed during your last visit
  - The study clinician may perform a vaginal exam to check that the vaginal ring is inserted correctly
  - Study staff will speak with you again and answer your questions about the rules of the study and wearing the vaginal ring, including keeping the vaginal ring in place, not removing it between visits, and recording any problems in your study product use log

Study staff will:

- Take a blood sample **[SITES TO INSERT AMOUNT]** for research purposes, to learn how dapivirine enters and exits the body over time.
- Ask you to express a breast milk sample. The milk collected will be used for research purposes only, to measure how dapivirine enters and exits the body over time, and may be tested for antiviral activity.
- Conduct a pelvic exam.
  - The study clinician will use a speculum.
- Give you any available test results

- Talk with you about any questions you have about contraception, if needed
- Reimburse you for your visit
- Schedule your next visit.

Study staff or you will:

- Collect cervicovaginal fluid samples via a swab. The fluid collected will be used for research purposes only.

### **AT-HOME BREAST MILK SAMPLING (Week 1):**

Between Visit 3 and Visit 4 (approximately 1 week later), you will be asked to collect breast milk samples away from the clinic -- either at home or at a location of your choosing. Study staff will provide you with supplies including a breast pump if you need it, plastic sample collection bags, and a collection log on which you will be asked to record when you collected the samples. For At-Home Breast Milk Sampling (Week 1), you will be asked to collect samples for 5 days (minimum of 2 samples per day). Study staff will provide you with more information about the sample collection schedule, how to use the pump and bags to collect your samples, and how to properly store the breast milk samples between visits. The milk collected will be used for research purposes only, to better understand how dapivirine enters and exits the body over time, antiviral activity, and how dapivirine affects milk fat. When these samples are collected during At-Home Breast Milk Sampling (Week 2), similar tests will be done. You will be asked to bring these samples and your collection log with you to your next visit. You must agree to not provide any breast milk you express to your child(ren) or anyone else, such as for immediate consumption, banking, or freezing.

### **Visit 4:**

Visit 4 will take place after you have worn the vaginal ring for about 1 week (approximately 7 days after your Enrollment visit). It will take between **[SITES TO SPECIFY TIMEFRAME]** to complete. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of mastitis or a urinary, genital, or other infection and/or other issues).

At Visit 4, study staff will collect from you:

- The breast milk samples you expressed at home
- The breast milk sample collection log
- The vaginal ring product use log

You will:

- Update study staff with your contact information

- Discuss any health or medical problems you may have had in the past or are currently experiencing or have occurred since your last visit (including what medications you are taking)

**Study staff will:**

- Talk with you about any problems you may be experiencing while wearing the vaginal ring or resulting from procedures performed during your last visit
  - The study clinician may perform a vaginal exam to check that the vaginal ring is inserted correctly
  - Study staff will speak with you about the rules of the study if you need a reminder.
- Ask you about your sexual practices
- Conduct a pelvic exam.
  - The study clinician will use a speculum.
- Take a blood sample **[SITES TO INSERT AMOUNT]** for research purposes, to learn how dapivirine enters and exits the body over time.
- Ask you to express a breast milk sample. The milk collected will be used for research purposes only.
- Give you any available test results
- Talk with you about any questions you have about contraception, if needed
- Reimburse you for your visit
- Schedule your next visit.

**Study staff or you will:**

- Collect cervicovaginal fluid samples via a swab. The fluid collected will be used for research purposes only.

**AT-HOME BREAST MILK SAMPLING (Week 2):**

Between Visit 4 and Visit 5, you will again be asked to collect breast milk samples at home. Study staff will provide you with additional supplies if needed. For At-Home Breast Milk Sampling (Week 2), you will be asked to collect samples for 6 days (minimum of 2 samples per day). Study staff will address any questions or problems you may have about the sample collection schedule, how to use the pump and bags to collect samples, and how to properly store the samples between visits. You will be asked to bring these samples and your collection log with you to your next visit.

**Visit 5:**

Visit 5 will take place after you have worn the vaginal ring for about 2 weeks (approximately 14 days after your Enrollment visit). It will take between **[SITES TO SPECIFY TIMEFRAME]** to complete. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of mastitis or a urinary, genital, or other infection and/or other issues).



At Visit 5, study staff will collect from you:

- The breast milk samples you expressed at home
- The breast milk sample collection log
- The vaginal ring product use log

You will:

- Update study staff with your contact information
- Discuss any health or medical problems you may have had in the past or are currently experiencing or have occurred since your last visit (including what medications you are taking)

Study staff will:

- Take a blood sample **[SITES TO INSERT AMOUNT]** for research purposes, to learn how dapivirine enters and exits the body over time.
- Ask you to express a breast milk sample, for research purposes
- Talk with you about any problems you experienced while wearing the vaginal ring or resulting from procedures performed during your last visit
- Ask you about your sexual practices
- Study staff will speak with you about the rules of the study if you need a reminder.
- The study clinician will remove the vaginal ring. Study researchers will keep the ring and may run additional tests on it for research purposes only
- You will have a pelvic exam
  - The study clinician will use a speculum.
- Give you any available test results
- Talk with you about any questions you have about contraception, if needed
- Reimburse you for your visit
- Schedule your next visit.

**Study staff or you will:**

- Collect cervicovaginal fluid samples via a swab. The fluid collected will be used for research purposes only.

### **AT-HOME BREAST MILK SAMPLING (After Ring Removal)**

Between Visit 5 and Visit 6, you will again be asked to collect breast milk samples, ideally at least 2 on Day 15, at home. Study staff will provide you with additional supplies if needed. You will be asked to bring these samples and your collection log with you to your next visit.

### **Final Visit/Termination (Visit 6):**

Your Final Visit will take place approximately 2 days (48 hours) after the vaginal ring is removed. This visit will take between **[SITES TO SPECIFY TIMEFRAME]** to

complete. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of mastitis or a urinary, genital, or other infection and/or other issues).

At this visit, you will:

- Update study staff with your contact information
- Discuss any health or medical problems you may have had in the past or are currently experiencing or have occurred since your last visit (including what medications you are taking)

Study staff will:

- Talk with you about any problems you experienced while wearing the vaginal ring or resulting from procedures performed during your last visit
- Ask you about your sexual practices
- Have your urine tested for pregnancy
- Take a blood sample **[SITES TO INSERT AMOUNT]** for research purposes, to learn how dapivirine enters and exits the body over time.
- Ask you to express a breast milk sample, for research purposes.
- A breast exam
- Conduct a pelvic exam.
  - The study clinician will use a speculum.
- Give you any available test results
- Talk with you about any questions you have about contraception, if needed
- Reimburse you for your visit
- Schedule your next visit or contact, if necessary.
- (If necessary) The study clinician will remove the vaginal ring, if it was not removed while you were at the clinic for Visit 5.
- (If necessary) Collect from you any remaining breast milk samples, the breast milk sample collection log, or the vaginal ring product use log if you were unable to bring them with you to other visits

**Study staff or you will:**

- Collect cervicovaginal fluid samples via a swab. The fluid collected will be used for research purposes only.

It is important that you remember that at any time during the study, study staff can answer any questions you may have about the procedures mentioned above.

#### Additional Visits and Procedures

It may be necessary for you to have additional visit(s) and/or provide additional samples if any of the above procedures need to be repeated due to issues with sample processing, testing or shipping, and/or if you are experiencing any symptoms or changes in your physical condition.

Additional testing may be performed as part of quality control.

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

Dapivirine is currently still being tested for HIV prevention, and the results are not yet out. 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. Tests may be performed to see if you have HIV drug resistance. This will allow doctors to know what HIV drugs would be best for the treatment of your type of HIV. If the HIV tests indicate you may be infected with HIV, you will stop using the vaginal ring. If HIV infection is confirmed, you will stop your participation in this study.

## **RISKS AND/OR DISCOMFORTS**

### **Risks of Blood Draws**

Whenever your blood is drawn, you may have:

- Excessive bleeding
- Discomfort or pain
- Feelings of dizziness or faintness
- Bruising or swelling
- A small clot and/or infection where the needle goes into your hand or arm

### **Risks of Genital Exams**

During pelvic exams and cervical and vaginal fluid collection you may feel discomfort or pressure in your vagina, genital area and/or pelvis. You may also have vaginal bleeding or spotting, which should stop shortly after the examination.

### **Risks of Breast Pump Use and Weaning**

Some women experience discomfort the first few times they pump, but pumping should never be painful, result in sore or irritated nipples, or cause bleeding. These may be signs of an injury, problems with your breast pump, or errors in pumping technique. If you experience these, or any other symptoms you are concerned about, please consult a member of the study staff.

Weaning from breastfeeding may be associated with breast discomfort and mixed feelings related to stopping breastfeeding.

### **Risks of Study Ring**

The study ring can cause some side effects, such as an allergic reaction. Signs of an allergic reaction include, but are not limited to: Rash or other skin irritation, itching, joint pain, or difficulty in breathing.

We do not yet know all the side effects of the ring. Some, but not all women who used the ring in other studies have had:

- Vaginal discharge
- Vaginal irritation
- Vaginal discomfort

### **Risks of Dapivirine**

Based on side effects reported among women in previous studies, dapivirine vaginal rings (VRs) may be associated with:

- Vaginal bleeding at irregular intervals, particularly between your expected menstrual periods
- Vaginal or genital discharge
- Yeast infection
- Urinary tract infection

### **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 you are HIV-positive could cause depression and/or suicidal thoughts. Finding out your HIV or STI 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.

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

The vaginal ring being tested in this study is not a birth control method. We do not know what effect dapivirine has on pregnancy, including the effect of dapivirine 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, anyone who is pregnant may not join this study. Participants who join the study must agree to use an effective method of contraception. Acceptable contraceptive methods in this

study include: hormonal methods (except for contraceptive vaginal rings); IUDs inserted at least 28 days prior to enrollment; you engage in sex exclusively with women; sterilization (you or your partner has been sterilized); and abstinence (you have been sexually abstinent for the past 90 days and intend to remain abstinent during your participation in the study). Participants who join this study will have pregnancy tests while in the study.

After you enroll in the study, any further milk that you express until involution (when the fullness of your breasts disappears and your breast size returns to normal after lactation ends) should be discarded, except for the samples collected for this research as described above. You must agree to not provide breast milk to your child(ren) or anyone else, such as for immediate consumption, banking, or freezing.

If you have more children in the future, you can reinstate breastfeeding as all of the dapivirine will have exited your body by that time.

### **BENEFITS**

No one knows if the study ring will prevent HIV infection. Although you may not experience any direct benefit from participation in this study, 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.

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. 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. 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 needed.

### **NEW INFORMATION**

You will be told of 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 MTN-029/IPM 039 study results are available, and how to learn about them. Additionally, you will be told of any new information about other effective HIV-prevention products as they become available.

### **WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT**

You may be removed from the study early without your permission if:

- The study is cancelled by the US FDA, US NIH, IPM (the nonprofit organization that supplies the vaginal rings), the US Office for Human Research Protections

(OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB). An IRB is a committee that watches over the safety and rights of research participants

- The Study Monitoring Committee (SMC) recommends that the study be stopped early (the SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study)
- You are found to be infected with HIV
- You become pregnant
- After enrolling in the study, you provide breast milk to your child(ren) or anyone else, for immediate consumption, banking, or freezing, or you express an intention to do so
- A study clinician decides that using the vaginal ring would be harmful to you, for example you have a bad reaction to the study ring
- Other reasons that may prevent you from completing the study successfully, such as you are not able to reliably keep appointments

If a study clinician asks you to stop using the ring, a few final procedures may take place, but you will no longer continue to come in for your regularly scheduled clinic visits.

In the event that you are removed from or choose to leave this study, you will be asked to return your vaginal ring and complete a final evaluation. 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. **[SITE 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, the breast pump and milk collection supplies, physical/pelvic examinations, laboratory tests or other procedures. Treatments available to you from the study site for infections passed through sex may be given to you free of charge or you will be referred for available treatment for the duration of the study.

### **REIMBURSEMENT**

**[SITE TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT]:** You will receive **[SITE TO INSERT AMOUNT \$XX]** for your time, effort, and travel to and from the clinic at each scheduled visit. You may receive **[SITE 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 may 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 Drug Administration (FDA), US Office for Human Research Protections (OHRP), NIH and/or contractors of NIH, and other local and US regulatory authorities
- Representatives of IPM, including study monitors
- PPD (a contract research organization that monitors clinical trials for safety and data quality)
- Site IRB/ECs
- Study staff

***[SITE TO INCLUDE/AMEND THE FOLLOWING]:***

**Following study participation in MTN-029 you may be referred to other research studies.**

***[SITE 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 obtained 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**

***[SITE 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. The U.S. National Institutes of Health (NIH) does not have a mechanism to pay money or give other forms of compensation for research related injuries. You do not give up any legal rights by signing this consent form.

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

**[SITE 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]**.



**CONSENT FOR LONG-TERM STORAGE AND FUTURE TESTING OF SPECIMENS**

There might be a small amount of blood, cervicovaginal fluid, and/or breast milk left over after we have done all of the study related testing. We would like to ask your permission to store these leftover samples and related health information for use in future studies. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range. If you agree, your samples and related health data will be stored safely and securely at facilities that 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. You can still enroll in this study if you decide not to have leftover samples stored for future studies. If you do not want the leftover samples stored, we will destroy them. The type of testing planned for your leftover specimens is not yet known, however samples may be used by the MTN Laboratory Center to complete additional quality assurance testing, ensuring that the tests work correctly and supply accurate data. No genetic testing on either a limited set or the full set of genes is planned for leftover specimens that are stored for the purposes of future research. It is important that you know that any future testing or studies planned for these specimens must be approved by an Institutional Review Board before they can be done. You can withdraw your consent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study. However, researchers will not be able to destroy samples or information from research that is already underway.

\_\_\_\_\_  
Initials and Date

I DO agree to allow my biological specimens and health data to be stored and used in future research studies.

\_\_\_\_\_  
Initials and Date

I DO NOT agree to allow my biological specimens and health data to be stored and used in future research studies.

## SIGNATURES- VOLUNTARY CONSENT

***[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 the study, please sign your name or make your mark below.

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Participant Name (print)	Participant Signature/Mark	Date
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Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
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Witness Name (print)	Witness Signature	Date
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