# MTN-036/IPM 047

# A Phase 1, Randomized Pharmacokinetics and Safety Study of Extended Duration Dapivirine Vaginal Rings

**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**
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**IND #: 108,743**

**Protocol Chair:**
**Albert Liu, MD, MPH**

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**MTN-036/IPM 047**

**A Phase 1, Randomized Pharmacokinetics and Safety Study of Extended Duration Dapivirine Vaginal Rings**

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## 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 |
| AUC | area under the curve |
| b.i.d. | *bis in die* (twice daily) |
| BRWG | Behavioral Research Working Group |
| BSWG | Biomedical Science Working Group |
| BV | bacterial vaginosis |
| CASI | computer assisted self-interview |
| CBC | complete blood count |
| CCR5 | C-C chemokine receptor type 5 |
| CDC | Centers for Disease Control and Prevention |
| CFR | Code of Federal Regulations |
| $C_{max}$ | maximum concentration |
| CMRB | Clinical Microbicide Research Branch |
| CONRAD | Contraception Research And Development |
| CRF | case report form |
| CRMS | Clinical Research Management System |
| CROI | Conference on Retroviruses and Opportunistic Infections |
| CRS | clinical research site |
| CT | *Chlamydia trachomatis,* chlamydia |
| CTA | Clinical Trial Agreement |
| CVF | cervicovaginal fluid |
| CVL | cervicovaginal lavage |
| CWG | Community Working Group |
| CXCR4 | C-X-C chemokine receptor type 4 |
| DAERS | DAIDS Adverse Event Reporting System |
| DAIDS | Division of AIDS |
| DLV | delavirdine |
| DNA | deoxyribonucleic acid |
| DPV | dapivirine |
| EAE | expedited adverse event |
| EC | Ethics Committee |
| $EC_{50}$ | median effective concentration |
| EDC | electronic data capture |
| EFV | efavirenz |
| EMBRACE | Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure |
| ENR | Enrollment |
| FAME | Film Antiretroviral Microbicide Evaluation |
| FDA | (US) Food and Drug Administration |
| FHCRC | Fred Hutchinson Cancer Research Center |
| g | grams |

| | |
|---|---|
| GC | *Neisseria gonorrhoeae,* gonorrhea |
| GCP | Good Clinical Practices |
| GMP | Good Manufacturing Practices |
| HEENT | Head, Eye, Ear, Nose and Throat |
| HHS | (US) Department of Health and Human Services |
| HIV | Human Immunodeficiency Virus |
| HPV | human papillomavirus |
| HSV | herpes simplex virus |
| hu-PBL | human peripheral blood lymphocytes |
| hu-SCID | humanized severe combined immunodeficiency |
| IATA | International Air Transport Association |
| IB | Investigator's Brochure |
| ICF | informed consent forms |
| ICH | International Conference on Harmonization |
| ICRC | International Committee of the Red Cross |
| IDI | in-depth interview |
| IND | Investigational New Drug |
| IoR | Investigator of Record |
| IP | Investigational Product |
| IPM | International Partnership for Microbicides |
| IRB | Institutional Review Board |
| IUD | intrauterine device |
| KOH | potassium hydroxide |
| LC | (MTN) Laboratory Center |
| LDMS | Laboratory Data Management System |
| LLOQ | lower limit of quantification |
| LOC | (MTN) Leadership and Operations Center |
| µg | microgram |
| µM | micromole |
| m | meter |
| mg | milligram |
| MIV-160 | (-)-cis-1-(5-Cyanopyridin-2-yl)-3-(4,7-diflouro-1,1a,2,7b-tetrahydrocyclopropa[c]chromen-1-yl)-urea, MSR-216; an NNRTI |
| mL | milliliter |
| mm | millimeter |
| MO | Medical Officer |
| MPID | Maternal and Pediatric Infectious Diseases |
| MTD | maximum tolerated dose |
| MTN | Microbicide Trials Network |
| NAAT | nucleic acid amplification test |
| ng | nanogram |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NICHD | *Eunice Kennedy Shriver* National Institute of Child Health and Human Development |
| NIH | National Institutes of Health |
| NIMH | National Institute of Mental Health |
| nM | nanomole |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NVP | nevirapine |
| OHRP | Office for Human Research Protections |
| PD | pharmacodynamics |
| PEP | post-exposure prophylaxis |
| pg | picogram |
| PID | pelvic inflammatory disease |
| PK | pharmacokinetics |
| PoR | Pharmacist of Record |
| PPD | Pharmaceutical Product Development |

| | |
|---|---|
| PrEP | pre-exposure prophylaxis |
| PRO | Protocol Registration Office |
| PSP | Prevention Sciences Program |
| PSRT | Protocol Safety Review Team |
| PTID | participant identification |
| PUEV | product use end visit |
| PVI | penile-vaginal intercourse |
| RE | Regulatory Entity |
| RF | rectal fluid |
| 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 |
| SCR | Screening |
| SDMC | Statistical Data Management Center |
| SMC | Study Monitoring Committee |
| SOC | System Organ Class |
| SOP | standard operating procedure |
| SSP | study specific procedures |
| STI | sexually transmitted infection |
| SUSARs | suspected, unexpected serious adverse reactions |
| TEAE | treatment-emergent adverse events |
| TMC-120 | dapivirine |
| UNAIDS | United Nations Programme on HIV/AIDS |
| UPMC | University of Pittsburgh Medical Center |
| USA | United States of America |
| UTI | urinary tract infection |
| VR | vaginal ring |
| WHO | World Health Organization |

**MTN-036/IPM 047**

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**MTN-036/IPM 047**

**A Phase 1, Randomized Pharmacokinetics and Safety Study of Extended Duration Dapivirine Vaginal Rings**

**INVESTIGATOR SIGNATURE FORM**
**Version 1.0; June 28, 2017**
**A Study of the Microbicide Trials Network**

**Funded by:**
Division of AIDS (DAIDS), 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 (NIH)

**IND Holder:**
International Partnership for Microbicides (IPM) (DAIDS Protocol ID: 30009)

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference for Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., NIH, DAIDS) and institutional policies.

I agree to maintain all study documentation for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. DAIDS will inform the investigator/institution as to when these documents no longer need to be retained.

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 (print)

_____ _____
Signature of Investigator of Record Date

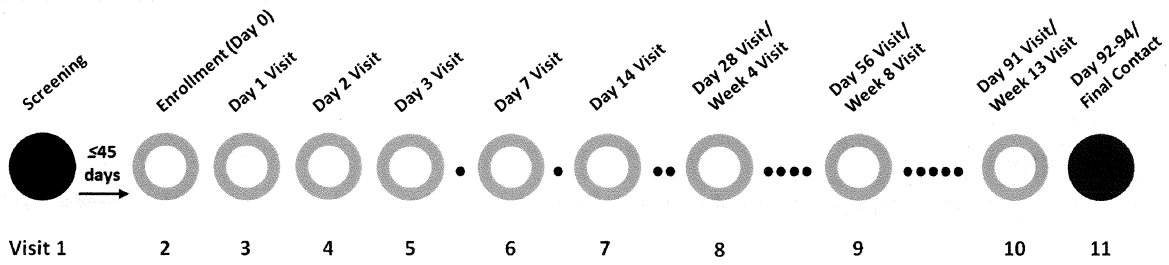
**MTN-036/IPM 047**

**A Phase 1, Randomized Pharmacokinetics and Safety Study of Extended Duration Dapivirine Vaginal Rings**

## PROTOCOL SUMMARY

| | |
|---|---|
| **Short Title:** | PK and Safety Study of Extended Duration DPV VRs |
| **Clinical Phase:** | Phase 1 |
| **IND Sponsor:** | IPM |
| **Protocol Chair:** | Albert Liu, MD, MPH |
| **Sample Size:** | Approximately 48 participants |
| **Study Population:** | Healthy, HIV-uninfected women and those assigned female sex at birth 18-45 (inclusive) years old |
| **Study Sites:** | US sites selected by the MTN Executive Committee |
| **Study Design:** | Phase 1, three-arm, multi-site, randomized (1:1:1) trial |
| **Study Duration:** | Accrual will require approximately 6-9 months. Participants will be followed for approximately 94 days. |
| **Study Products:** | Three silicone elastomer vaginal rings (VRs) containing either:<br>• 25 mg of the active ingredient dapivirine (DPV; IPM Ring-004 [Comparator VR])<br>• 100 mg DPV (IPM Ring-008)<br>• 200 mg DPV (IPM Ring-006) |
| **Study Regimen:** | Participants will be randomized to one of three study VRs in a 1:1:1 ratio, and those randomized to the 100 mg and 200 mg VRs will not be told their group assignment. Participants will insert one VR to be used continuously for 13 weeks (100 mg VR or 200 mg VR) or one VR (25 mg VR) to be replaced every 4 weeks for 8 weeks, then worn for an additional 5 weeks for a total of 13 weeks. Participants will continue follow-up for an additional one to three days after final VR removal. |

**Figure 1: Study Visit Schedule**




## Primary Objectives:

### Pharmacokinetics

- To compare the local and systemic pharmacokinetics (PK) of two extended duration DPV VRs (100 mg and 200 mg) when used continuously for 13 weeks to the current 25 mg DPV VR when replaced every 4 weeks for 8 weeks and then worn for an additional 5 weeks for a total of 13 weeks

### Safety

- To compare the safety of the two extended duration DPV VRs (100 mg and 200 mg) to the current 25 mg DPV VR when used for 13 weeks

## Primary Endpoints:

### Pharmacokinetics

- DPV concentrations in plasma
- DPV concentrations in cervicovaginal fluid
- DPV concentrations in cervical tissue

### Safety

- Proportions of participants with Grade 2 or higher genitourinary adverse events as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, March 2017, and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])
- Proportions of participants with Grade 3 or higher adverse events as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, March 2017

**Secondary Objectives:**

**Adherence**

- To evaluate participant adherence to the three DPV VRs when used for 13 weeks

**Acceptability**

- To compare overall acceptability of the two extended duration DPV VRs (100mg and 200 mg) to the current 25 mg DPV VR

**Secondary Endpoints:**

**Adherence**

- Frequency of study VR removal/expulsions (voluntary and involuntary) and duration without VR in vagina (by self-report)
- VR use initiation and persistence (whether the VR is in place when participants come to the clinic for their study visits)

**Acceptability**

- Degree to which study participants liked or disliked using the three DPV VRs (by self-report)

**Exploratory Objectives:**

**Vaginal Microenvironment**

- To describe the genital microenvironment in HIV-uninfected women and those assigned female sex at birth using a DPV VR for 13 weeks

**Pharmacokinetics**

- To compare the rectal compartment PK of the two extended duration DPV VRs (100mg and 200 mg) when used continuously for 13 weeks to the current 25 mg DPV VR

**Adherence**

- To evaluate markers of ring use for the three DPV VRs

**Acceptability**

- To evaluate components of acceptability of ring use for the three DPV VRs

**Exploratory Endpoints:**

**Vaginal Microenvironment**

- Changes in microbiota and biomarkers during DPV VR use

**Pharmacokinetics**

- DPV concentrations in rectal fluid

**Adherence**

- Plasma DPV levels
- Residual DPV levels in returned VRs

**Acceptability**

- Self-reported attitudes about VR attributes, including dosing regimen, and willingness to use the VR in the future
- Interest/preference in a single vs. dual-purpose indication
- Proportion of participants who find the study VRs to be at least as acceptable as other HIV prevention methods

# 1 KEY ROLES

## 1.1 Protocol Identification

| | |
|---|---|
| Protocol Title: | A Phase 1, Randomized Pharmacokinetics and Safety Study of Extended Duration Dapivirine Vaginal Rings |
| Protocol Number: | MTN-036/IPM 047 |
| Short Title: | PK and Safety Study of Extended Duration DPV VRs |
| Date: | June 28, 2017 |

## 1.2 Funding Agencies, Sponsor and Monitor Identification

| | |
|---|---|
| Funding Agencies: | US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID)<br>National Institutes of Health (NIH)<br>6700 B Rockledge Drive<br>Rockville, MD 20852 USA<br><br>US National Institute of Mental Health (NIMH)<br>6001 Executive Boulevard<br>Rockville, MD 20852 USA<br><br>US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)<br>Maternal and Pediatric Infectious Diseases (MPID) Branch<br>6100 Executive Boulevard<br>Bethesda, MD 20892 USA |
| IND Sponsor: | International Partnership for Microbicides (IPM)<br>8405 Colesville Rd., Suite 600<br>Silver Spring, MD 20910 USA |
| Monitor: | Pharmaceutical Product Development (PPD), Inc.<br>929 North Front St.<br>Wilmington, NC 28401-3331 USA |

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# 2 INTRODUCTION

## 2.1 Microbicides in HIV/AIDS Prevention

In 2014, 2 million people were newly infected and 1.2 million lost their lives to human immunodeficiency virus (HIV)-related causes.[1] Every 60 seconds, a young woman is infected with HIV.[2] Women and girls continue to be affected disproportionately by HIV in sub-Saharan Africa, where women account for approximately 60% of people living with HIV.[3] The ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to under-resourced countries remains a public health priority.

Unprotected heterosexual intercourse is the leading mode of HIV acquisition among women. Correct and consistent use of latex condoms is one proven method of preventing HIV acquisition; however, since many women may be unable to negotiate condom use with their partners, condom use is regarded as an inadequate prevention option for women. Thus, developing HIV prevention options that women can use independent of male partner consent 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,[4, 5] 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 effective, it is essential that it is used correctly and consistently, and is also acceptable to the user. In addition, a product used independently of sex 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 to help prevent HIV acquisition. 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 or less frequently may have benefits over dosage forms that need to be used more frequently.

Multiple clinical trials have evaluated the safety of dapivirine (DPV) in VRs,[6] aqueous gels,[7-10] quick-dissolve vaginal films[7-9] and in an oral[11, 12] formulation. These clinical trials support the favorable safety profile and tolerability of DPV in general and specifically in vaginal delivery formulations. The safety and efficacy of the VR containing DPV 25 mg (Ring 004) replaced monthly were recently tested in two randomized, double-blind, placebo-controlled Phase 3 trials: MTN-020 (ASPIRE) and IPM 027 (The Ring Study).

Both trials demonstrated that the VR was safe and effective for prevention of HIV-1 acquisition.[13, 14]
The development of a VR with a higher DPV loading dose may allow less frequent VR replacements (e.g., quarterly basis instead of monthly basis) that may further reduce patient and provider burden, streamline follow-up, and improve adherence.

MTN-036/IPM 047 is a collaboration between the Microbicide Trials Network (MTN) and IPM to evaluate the pharmacokinetics (PK) and safety of two extended duration DPV VRs (loaded with 100 mg and 200 mg DPV), as compared to the current 25 mg monthly ring tested in ASPIRE and The Ring Study.

## 2.2 Dapivirine

### 2.2.1 Description

DPV (also known as TMC-120), a non-nucleoside reverse-transcriptase inhibitor (NNRTI), is a substituted di-amino-pyrimidine derivative with potent antiviral activity against HIV-1. DPV is chemically described as 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile.[15]

Three VRs composed of platinum-catalyzed cured silicone matrix using polymer 4870 and containing three different loading doses of DPV (25, 100 and 200 mg) will be used in this trial. The VR containing 25 mg of DPV is known as Ring-004; the VR containing 100 mg of DPV is known as Ring-008; and the VR containing 200 mg of DPV is known as Ring-006. When delivered via VR, DPV has demonstrated favorable local and systemic safety and PK profiles as described below.

DPV 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.[16] DPV is a promising topical microbicide candidate due to its proven *in vitro* and *in vivo* efficacy, favorable safety profile, and its physical and chemical properties.[6, 10, 15, 17] DPV has potent activity against wild-type HIV-1 strains and strains harboring different resistance-inducing mutations.[6, 10, 15, 17] The ARV profile of DPV 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 DPV is not active against HIV-2 and has little or no activity against common sexually transmitted infections (STIs). Therefore it is not intended for use against HIV-2 or other STIs. DPV does not have any contraceptive properties.[18] The DPV VR, gel and film are intended to be used as complementary prevention technologies to male and female condoms.[6] Detailed information on DPV is available in the DPV VR Investigator's Brochure (IB).[6]

IPM has investigated a wide range of dosage forms for the development of topical microbicide products, including vaginal gels, VRs, films, tablets and soft gel capsules. Vaginal gel was the initial dosage form chosen for a DPV-based microbicide because the

majority of previous microbicides evaluated in clinical trials were vaginal gels. Therefore, a wealth of information was available on this dosage form. However, the silicone elastomer matrix VR has been prioritized over all other dosage forms for the following reasons:

- Clinical trials have demonstrated sustained delivery of high levels of DPV 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 in women using VRs with similar physical characteristics;
- The overall cost for the VR is relatively low;
- The VR requires minimal storage space when compared to once daily products;
- VR use may be extended beyond 28 days with this inert study delivery device.

Summaries of the safety and tolerability of DPV administered orally and vaginally as evaluated in clinical studies by IPM and Janssen Research and Development can be found in Section 2.4.

### 2.2.2 Mechanism of Action

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

### 2.2.3 Strength of Study Product

The study VRs will contain either 25 mg, 100 mg or 200 mg of DPV.

## 2.3 Nonclinical Studies of Dapivirine

### 2.3.1 In vitro Studies of Dapivirine

**Anti-HIV-1 Activity**

The antiviral activity of DPV against wild-type HIV-1, clinical isolates of HIV-1 (including subtype C virus), and a panel of NNRTI-resistant viruses has been established using *in vitro* models. The median effective concentration ($EC_{50}$) 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.[6]

The anti-HIV activity of DPV as a microbicide was confirmed in an *ex vivo* model of human cervical and colonic explant cultures[15]. DPV potently inhibited HIV-$1_{BaL}$ (R5) infection of human ectocervical tissue explants in a dose-dependent manner ($IC_{50}$ = 1.5 nM [0.49 ng/mL]). Although complete inhibition of integrated provirus was not observed at all

concentrations, greater than 99% inhibition was observed at concentrations down to 10 nM (3.3 ng/mL). Furthermore, in this model 100 nM (32.9 ng/mL) DPV was able to block transfer of free virus by migratory dendritic cells to indicator T-cells ($IC_{50}$ = 0.1 nM [0.03 ng/mL]).[6] Pre-treatment of ectocervical tissue with DPV for 2 or 24 hours inhibited HIV-1 infection when challenged with virus on Days 0, 2, 4 and 6 post drug removal. DPV was also able to inhibit virus dissemination by migratory cells for up to 6 days post drug removal at concentrations as low as 3.3 µg/mL (10 µM) following treatment for 2 or 24 hours. Formulated DPV showed retention of activity by blocking HIV infection of ectocervical tissue at 10 µM and colonic tissue at 1 µM.[19] In vitro testing showed DPV retained activity in the presence of semen, with a similar $EC_{50}$ of 1.95 nM without and 1.7 nM with semen.[19]

**Resistance**

HIV-1 breakthrough in the presence of DPV 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 DPV. At DPV 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 DPV. Subsequently, cells were infected with wild-type HIV-1 at low multiplicity of infection and were exposed to very low concentrations of DPV to mimic the extremely low systemic concentrations observed in the first clinical trial of topical DPV gel (Gel-001).[6]

Population sequencing performed following prolonged exposure of HIV-1 LAI-infected MT4 cells to low concentrations of DPV for a period of approximately 30 days identified several NNRTI resistance-associated mutations, including Y181C, at DPV 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 further experiments using the same and lower DPV concentrations, population sequencing identified the Y181C mutation at 1 nM, but not at lower concentrations. Analysis using more sensitive single genome sequencing indicated the presence of Y181C at 0.1 nM, and possibly 0.01 nM (approximately 10-fold lower than the $EC_{50}$ for DPV).[6]

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 DPV can result in selection of viruses carrying NNRTI resistance-associated mutations, but the clinical relevance of these in vitro data is not known.[6]

Experiments comparing the selection of resistant viruses following exposure to DPV vs. the NNRTIs UC781, MIV-160, NVP and EFV showed that DPV 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, EFV and NVP was detected within 5 weeks. Other mutations selected under DPV pressure included E138Q, K101E, V108I, K103N, Y181C, V179M/E and F227Y.[6]

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 DPV-resistant form of VI829.[6]

**Cross-resistance**

In comparison with NVP, DLV, EFV and emivirine, DPV showed significantly better *in vitro* activity against laboratory and recombinant HIV strains resistant to one or more drugs of the same class. The $EC_{50}$ was below 32.9 ng/mL (100 nM) for 80% of the strains compared with only 56% of the strains for EFV. When tested against 433 clinical isolates with phenotypic resistance to at least one of the NNRTIs NVP, DLV, EFV or DPV, DPV 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 DPV-resistant strains were inhibited by EFV.[6]

**Condom Compatibility Studies of Dapivirine**

Chemical compatibility studies with different DPV-containing gel formulations have been conducted on the following types of condoms:[6]

- 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 DPV-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.[6]

**Drug Release Testing**

*In vitro* release testing performed by IPM during VR formulation development demonstrated that VRs composed of polymer Nusil® MED-4870 carrying the 100 mg and 200 mg DPV doses to be tested in MTN-036/IPM 047 provided high sustained release and high levels of DPV.[20] For example, in *in vitro* release testing of VRs containing dapivirine 100, 150 and 200 mg conducted over 60 days, each ring tested exceeded the *in-vitro* release target for dapivirine (200 µg at day 60). Day 60 dapivirine release was 284-285 µg, 363-376 µg, and 437-454 µg for the 100, 150 and 200 mg dapivirine VRs, respectively.[21], [20] This is the same polymer used in the 25 mg DPV VR shown to be safe and well-tolerated in two Phase 3 trials, ASPIRE and The Ring Study[13, 14]. The anticipated drug exposure due to the release from the 100 and 200 mg DPV VRs is expected to fall within pre-established preclinical and clinical safety margins for which vaginally administered data exist. In an *in-vitro* study with a duration of 92 days, formulations composed of the Nusil® MED-4870 polymer and containing 200 mg dapivirine exceeded the target daily release rate of 200 µg/day (d30 = 628 µg/day; d60 = 437 µg/day; d92 = 301/day µg), [22] which is less than 1.25 mg/day, the maximum daily dose observed in DPV vaginal gels (Gel 4750, Gel 4789 and Gel 4759).[6] See Section 2.4.2 for additional information.

### 2.3.2 Animal Studies of Dapivirine

**Anti-HIV-1 Activity**

The anti-HIV activity of DPV as a microbicide was confirmed in a humanized severe combined immunodeficient (hu-SCID) mouse model. DPV blocked vaginal transmission of HIV-1 in a hu-SCID mouse model in which animals received a single vaginal application of DPV gel prior to a non-invasive vaginal challenge with human peripheral blood lymphocytes (hu-PBL) previously infected *in vitro* with CCR5-tropic and dual tropic (CCR5/CXCR4) HIV-1 strains. DPV prevented a systemic infection with either CCR5 or CCR5/CXCR4 virus strains at concentrations of 2.25 µM (0.7 µg/mL) and higher. The efficacy rate ranged from approximately 70 to 100%, depending on the vaginal gel formulation. The protection resulted directly from the ARV activity of DPV.[6]

**Pharmacokinetics**

A PK study was conducted in sheep: DPV rings were inserted vaginally for up to 15 days and vaginal fluid and plasma concentrations were determined. Systemic exposure to DPV showed little change with increasing DPV ring loads (Table 1). In vaginal fluid, maximum concentration ($C_{max}$) and area under the curve (AUC) values for DPV were higher for rings containing 200 or 530 mg DPV than the ring containing 75 mg DPV.[23]

**Table 1: Pharmacokinetics of Dapivirine in Plasma and Vaginal Fluid Following Vaginal Administration of DPV VRs in Sheep**

| Ring Load (mg) | Plasma | | | Vaginal Fluid | | |
|---|---|---|---|---|---|---|
| DPV | $C_{max}$ (pg/mL) | $AUC_{0\text{-last}}$ (pg.h/mL) | $T_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_{0\text{-last}}$ (ng.h/mL) | $T_{max}$ (h) |
| 75 | 91.3 | 26201 | 72 | 1470 | 31447 | 6 |
| 200 | 99.8 | 23635 | 12 | 2840 | 212896 | 6 |
| 530 | 94.2 | 24559 | 12 | 2046 | 108163 | 6 |

**Safety**

A 13-week vaginal study was conducted in female rats in which gels comprising the same formulation as Gel 4759, but containing 0.2% and 0.5% DPV, were administered daily. No evidence of local or systemic toxicity was observed. [6]

A 13-week study in rabbits was performed using Gel 4789 containing 0.05 or 0.2% DPV that had been aged artificially at 40°C at 75% relative humidity in order to increase the impurities to levels adequate to provide qualification of concentrations likely to occur in gels for clinical use. No evidence of local or systemic toxicity was observed. [6]

A safety study in pigtailed macaques was performed in which the DPV film (1.6 mg) was inserted daily for five days (Monday to Friday) one week, followed by four days (Monday to Thursday) the next week. Colposcopic examinations revealed no evidence of product-related tissue disruption. The DPV film did not adversely affect vaginal flora, with no pattern of decimation or overgrowth of any species. A minor and transient decrease in vaginal pH was seen with the DPV and a placebo film, and increases in polymorphonuclear cell counts, determined from Gram stained vaginal smears, were seen in a similar number of macaques treated with dapivirine and placebo films. [6]

## 2.4 Clinical Studies of Dapivirine

### 2.4.1 Clinical Studies of Dapivirine Vaginal Rings

To date, 27 Phase 1 and Phase 1/2 clinical trials of DPV with various dosage forms have been completed. These include eight trials of DPV VRs in 469 participants (DPV rings, n=298; placebo rings, n=183); eight trials of DPV vaginal gel in 774 participants (DPV gel, n=491; placebo gel, n=283); and 11 trials of oral DPV (oral DPV, n=211 participants).[6]

Additionally, two pivotal randomized, double-blind, placebo-controlled, Phase 3 trials (IPM 027 and MTN-020) were recently completed. The studies evaluated the long term safety and efficacy of the 25 mg DPV VR (Ring-004) for the prevention of HIV-1 acquisition in 4588 healthy, sexually active, HIV-uninfected women 18 to 45 years of age. The VR was replaced monthly.[13, 14]

**IPM 027** (The Ring Study) was conducted from March 2012 to December 2016 in South Africa and Uganda.[14] A total of 1959 women from South Africa (n=1762) and Uganda (n=197) were enrolled in the trial. Study participants were randomized in a 2:1 ratio to receive either a DPV VR or a placebo VR monthly over a fixed 2-year follow-up period.[14]

**MTN-020** (ASPIRE) was conducted from August 2012 to June 2015 in Malawi, South Africa, Uganda, and Zimbabwe.[13] A total of 2629 women from Malawi (n=272), South Africa (n=1426), Uganda (n=253), and Zimbabwe (n=678) were enrolled in the trial. Study participants were randomized in a 1:1 ratio to receive either a DPV VR or a placebo VR monthly. Median follow-up was 1.6 years (interquartile range, 1.1 to 2.3).[13]

In the 12 DPV VR trials completed to date (summarized in Table 2 below), two were conducted with reservoir configuration VRs (Rings 001 and 002), and one included both a reservoir VR (Ring 002) and a matrix ring with tin-catalyzed silicone curing (Ring-003).[6] The remaining nine trials, including the two efficacy studies, were conducted using a matrix ring with platinum–catalyzed silicone curing (Ring-004) which will be the comparator ring used in this trial.[24]

**Table 2: Phase –1-3 Clinical Trials of Dapivirine Vaginal Rings**

| Trial Details[6] | | | Number of Participants | | | | |
|---|---|---|---|---|---|---|---|
| Trial Number | Description | Duration | 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 | 12 | -- | -- | -- | 12 (crossover) |
| IPM 008 | Safety and PK in women | 7 days | -- | 10 | -- | -- | 3 |
| IPM 013 | Safety and PK in women | 56/57 days | -- | -- | -- | 36 | 12 |
| IPM 015 | Safety and PK in women | 84 days | -- | -- | -- | 140 | 140 |
| IPM 018 | Safety and PK in women | 28 days | -- | 8 | 8 | -- | 8 |
| IPM 024 | Safety and PK in women | 28 days | -- | -- | -- | 8 | 8 |
| IPM 028 | Drug-drug interaction potential with miconazole nitrate in women | 28 days | -- | -- | -- | 36 (crossover) | -- |
| IPM 034 | Safety and PK in women | 7, 14, 28, 56, or 84 days | -- | -- | -- | 40 | -- |
| IPM 027 | Safety and efficacy in women | 24 months | -- | -- | -- | 1307## | 652 |
| MTN-013 | Safety and PK/Pharmaco-dynamics (PD) of DPV/Maraviroc | 28 days | -- | -- | -- | 12 | 12 |
| MTN-020 | Safety and effectiveness in women | 2 years | -- | -- | -- | 1313 | 1316 |
| MTN-024 | Safety in post-menopausal women | 12 weeks | -- | -- | -- | 72 | 24 |
| TOTAL 5139 participants | | | 12 | 18 | 8 | 2964 | 2187 |

* Tin-catalyzed matrix ring
** Platinum-catalyzed matrix ring
## One participant randomized to Ring-004 did not receive the investigational product (IP) and had to withdraw from the trial prior to ring insertion.

### 2.4.2 Pharmacokinetics of Dapivirine

**DPV Gel and Oral Dosage Forms:**
Following single and multiple oral doses of DPV, maximum plasma concentrations were generally reached 1 to 3 hours after dose intake. Participants were exposed to oral doses of DPV ranging from 50 mg to 1000 mg daily. At the maximum tolerated dose (MTD) (multiple doses) of 300 mg twice daily (b.i.d.) for 14 days, $C_{max}$ plasma concentration was 2286 ng/mL and $AUC_{0\text{-}12h}$ was 18247 ng.h/mL.[23]

Of the multiple DPV gel dosage forms developed (i.e., Gel 4750, Gel 4789 and Gel 4759), the highest daily dose of DPV delivered from a vaginal gel was approximately 1250 µg/day.[10], This dose is 280 times lower than the MTD (single dose) for oral DPV (350 mg) and 480 times lower than the MTD (multiple doses) for oral DPV (300 mg twice daily for 14 days).[10] The MTD (single dose) and MTD (multiple doses) are more than 3000 times and 1200 times higher, respectively, than the mean $C_{max}$ (705 pg/mL to 716 pg/mL) and $AUC_{0\text{-}24h}$ (approximately 15 ng.h/mL) values following once daily application of Gel 4789 and Gel 4750 (both 0.05% DPV, 2.5 g) for 10 days. The MTD (single dose) and MTD (multiple doses) are also more than 5800 times and 2100 times higher, respectively, than the maximum mean $C_{max}$ (392 pg/mL) and $AUC_{0\text{-}24h}$ (8.4 ng.h/mL) values observed in women using DPV Ring-004 for 28 days (across IPM 013 and IPM 024).[10] These data suggest a wide safety margin when comparing the highest reported systemic exposures of orally administered and vaginally administered DPV. Across all completed trials with various DPV gel formulations, plasma concentrations of DPV were very low (≤ 2.33 ng/mL),[10] and were therefore well below plasma concentrations observed at the MTD for multiple oral doses (300 mg b.i.d. for 14 days; plasma $C_{max}$ of 2286 ng/mL).[10]

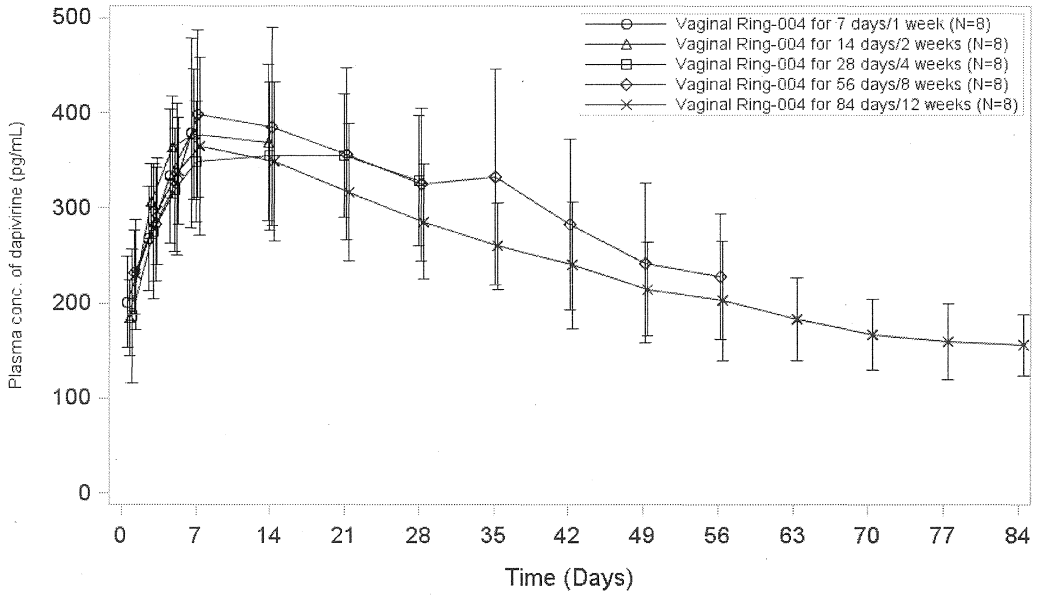
**Dapivirine VRs: DPV 25 mg VR (Ring-004)**
The PK profile of the DPV 25 mg VR (Ring-004) was evaluated in several Phase 1/2 studies which are detailed below.

**IPM 034** was a Phase 1, single center, open label, parallel group trial that enrolled 32 women into five groups (Groups A, B, C, D and E). Each woman was administered one DPV VR 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). Blood and vaginal fluid sampling for PK assessments of DPV were performed pre-dose (prior to ring insertion), at 4 h, 24 h, and on Days 3, 5, 7 (Groups A to E), Day 14 (Groups B to E), Days 21, 28 (Groups C to E), Days 35, 42, 49, 56 (Groups D and E), Days 63, 70, 77 and 84 (Group E) post-ring insertion. Residual levels of DPV in used/returned rings were assessed.[6]

Quantifiable DPV concentrations in plasma (lower limit of quantification [LLOQ] = 3.00 pg/mL) and vaginal fluid (cervix) (LLOQ = 0.4 ng per sample) were observed at the first sampling time of 4 hours after IP administration for all five treatment groups. Based on the mean concentration-time profiles, maximum plasma concentrations of DPV were achieved approximately 1 week after VR insertion and these concentrations remained fairly constant for the subsequent 2 weeks (see Figure 2). Thereafter, plasma

concentrations declined gradually to reach a mean plasma concentration of about 160 pg/mL 12 weeks after ring insertion. Within each treatment group the inter-subject variability was low.[6]

**Figure 2: Mean Plasma Concentration-Time Curves of Dapivirine (pg/mL) after Insertion of the Dapivirine Vaginal Ring-004 for 7, 14, 28, 56, or 84 Days (Groups A, B, C, D, and E): Mean ± SD Values**




Mean DPV $C_{max}$ was similar for all treatment arms and ranged from 385 to 449 pg/mL (Table 3). Median $t_{max}$ values were more variable and ranged from 168 h (7 days) to 420 h (17.5 days). Mean $C_{prior\ to\ ring\ removal}$ was similar for the DPV rings inserted for 1, 2 or 4 weeks, ranging from 329 to 379 pg/mL. For ring use periods of greater than 4 weeks the mean $C_{prior\ to\ ring\ removal}$ showed a more pronounced decline with duration of ring use, decreasing from 228 pg/mL at 8 weeks to 156 pg/mL at 12 weeks. These results suggest that an almost constant plasma level was maintained between 1 to 4 weeks after insertion of the ring. Mean AUCs for the different insertion durations were very similar between the different treatment groups. For each parameter within a treatment group, between-subject variability (% coefficient of variation [%CV]) was relatively low. Across all treatments and parameters %CV ranged from 13.1 to 29.1%.[6]

**Table 3: Pharmacokinetics of Dapivirine in Plasma and Vaginal Fluids (Cervix) after Insertion of the Dapivirine Vaginal Ring-004 for 7, 14, 28, 56, or 84 Days (Groups A, B, C, D, and E)**

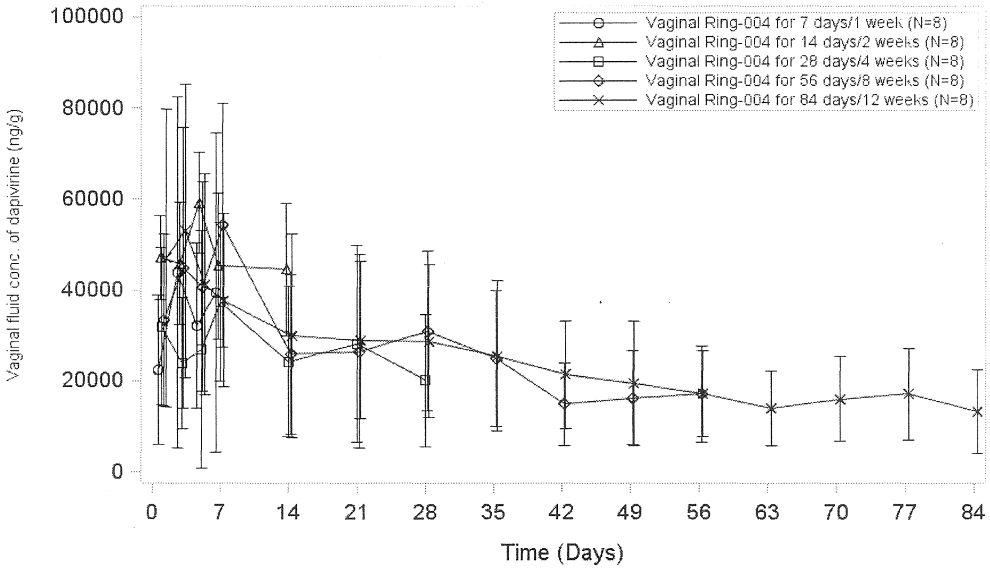
| ***Fluid Type*** PK Parameter (mean [± SD], $t_{max}$: median [range]) | **Group A (7 days/ 1 week ring insertion)** | **Group B (14 days/ 2 weeks ring insertion)** | **Group C (28 days/ 4 weeks ring insertion)** | **Group D (56 days/ 8 weeks ring insertion)** | **Group E (84 days/ 12 weeks ring insertion)** |
|---|---|---|---|---|---|
| ***Plasma*** | | | | | |
| n* | 8 | 8 | 8* | 8 | 8 |
| $C_{max}$ (pg/mL) | 385 (93.9) | 408 (67.1) | 389 (76.1) | 449 (83.7) | 393 (88.6) |
| $t_{max}$ (h) | 167.84 (119.45 - 168.13) | 169.29 (119.33 - 336.80) | 419.70 (71.73 - 672.47) | 252.86 (168.82 - 841.17) | 251.54 (71.75 - 503.77) |
| $C_{prior\ to\ ring\ removal}$ (pg/mL) | 379 (99.5) | 369 (82.0) | 329 (68.7) | 228 (66.5) | 156 (32.0) |
| $AUC_{0\text{-}7days}$ (pg.h/mL) | 45871 (9626) | 48698 (6375) | 43966 (9747) | 48384 (10032) | 48316 (8307) |
| $AUC_{0\text{-}14days}$ (pg.h/mL) | - | 111360 (17043) | 103233 (18544) | 114310 (24872) | 108291 (21136) |
| $AUC_{0\text{-}28days}$ (pg.h/mL) | - | - | 219747 (38717) | 234045 (53357) | 214841 (40726) |
| $AUC_{0\text{-}35days}$ (pg.h/mL) | - | - | - | 289359 (61233) | 260716 (48646) |
| $AUC_{0\text{-}42days}$ (pg.h/mL) | - | - | - | 341066 (71353) | 302719 (57481) |
| $AUC_{0\text{-}56days}$ (pg.h/mL) | - | - | - | 424686 (96618) | 376425 (75342) |
| $AUC_{0\text{-}84days}$ (pg.h/mL) | - | - | - | - | 491981 (95700) |
| ***Vaginal Fluid (Cervix)*** | | | | | |
| n* | 8 | 8 | 8* | 8 | 8 |
| $C_{max}$ (µg/g) | 53.1 (35.1) | 61.3 (10.4) | 48.2 (13.7) | 58.8 (22.7) | 59.2 (30.6) |
| $t_{max}$ (h) | 95.94 (24.02 - 168.17) | 119.86 (4.10 - 337.07) | 120.12 (4.00 - 503.82) | 168.87 (4.07 - 169.00) | 71.76 (3.95 - 672.13) |
| $C_{prior\ to\ ring\ removal}$ (µg/g) | 39.5 (35.1) | 44.6 (14.6) | 20.1 (14.7) | 17.2 (10.7) | 13.3 (9.23) |
| $AUC_{0\text{-}7days}$ (µg.h/g) | 5569 (3472) | 8168 (1610) | 4663 (2192) | 6943 (3685) | 7448 (4277) |
| $AUC_{0\text{-}14days}$ (µg.h/g) | - | 15709 (3945) | 9838 (4302) | 13671 (7039) | 13137 (7364) |
| $AUC_{0\text{-}28days}$ (µg.h/g) | - | - | 18376 (9662) | 22921 (12155) | 22957 (12377) |
| $AUC_{0\text{-}35days}$ (µg.h/g) | - | - | - | 27626 (14553) | 27511 (14767) |
| $AUC_{0\text{-}42days}$ (µg.h/g) | - | - | - | 30972 (16270) | 31455 (16913) |
| $AUC_{0\text{-}56days}$ (µg.h/g) | - | - | - | 36414 (18999) | 38011 (20642) |
| $AUC_{0\text{-}84days}$ (µg.h/g) | - | - | - | - | 48489 (25527) |

* n = 7 for $C_{prior\ to\ ring\ removal}$ and $AUC_{0\text{-}28days}$

For vaginal fluid levels (collected at the cervix), the mean concentration-time curves showed that maximum vaginal fluid concentrations were achieved after approximately 1

week (Figure 3). Thereafter, vaginal fluid concentrations declined gradually to reach a mean concentration of about 13 µg/g 12 weeks after ring insertion. Variability within and between participants was considerable, especially in the first week after ring insertion.[6]

**Figure 3: Mean Vaginal fluid Concentration-Time Curves of Dapivirine (ng/g) after Insertion of the Dapivirine Vaginal Ring-004 for 7, 14, 28, 56, or 84 Days (Groups A, B, C, D, and E): Mean ± SD Values**




Mean DPV $C_{max}$ in vaginal fluid was similar for all treatments and ranged from 48.2 to 61.3 µg/g (Table 3).[23] Median $t_{max}$ values ranged from 71.76 (3 days) to 168.87 h (7 days).[6] Mean $C_{\text{prior to ring removal}}$ was similar for the DPV rings inserted for 1 or 2 weeks, with values of 39.5 and 44.6 µg/g, respectively. For longer insertion durations, mean $C_{\text{prior to ring removal}}$ declined with duration of ring use: 20.1 µg/g at Week 4; 17.2 µg/g at Week 8; 13.3 µg/g at Week 12.[23] This suggests that an almost constant DPV vaginal fluid level was maintained 1-2 weeks after insertion of the ring. The lowest concentration observed after 12 weeks (prior to ring removal) was 1.138 µg/g, which was well above the *in vitro* concentration at which greater than 99% inhibition of integrated provirus was observed (3.3 ng/mL) in cervical tissue following challenge with HIV- 1BaL.[23]

**DPV Ring Residual Levels:** The mean residual levels of DPV in used rings were 16.8, 21.6, 20.1, 17.0, and 15.0 mg for Groups A to E, i.e. for rings used for 7, 14, 28, 56, and 84 days, respectively. The residual levels of DPV in the used rings decreased with duration of ring use, except for Group A (7 days insertion).[6] When extending the ring use period of Ring-004 to 56 and 84 days, on average, 8-10 mg of DPV was released over 56 to 84 days (8 to 12 weeks). The ring residual levels of DPV as determined in this clinical trial should be regarded as exploratory, as data for the rings from participants in Group A and Group B were brought into question based on the data of the control ring that yielded a low recovery value and which was analyzed simultaneously with the rings from the 16 participants in these groups. Upon exclusion of the Group A and Group B data, the trend

of decreasing residual amounts of DPV with increasing duration of ring use was consistent.[6]

In general, plasma $C_{\text{prior to ring removal}}$ and residual levels of DPV in used rings decreased linearly with duration of ring use, except for Group A. Though this linear decrease was more pronounced for plasma, the same trend was observed for vaginal fluid. When the results from Group A and Group B were excluded, the linear decrease was more clearly evident for plasma, with correlation coefficients ($r^2$) of 0.3 including the unreliable results and 0.6 excluding the unreliable results. Results for vaginal fluid were less clear, with correlation coefficients of 0.1 including the unreliable results and $5x10^{-5}$ excluding the unreliable results.[6]

A linear decrease in residual levels of DPV in used rings correlated with increases in $AUC_{0\text{-tdays}}$, for both plasma and vaginal fluid, and was associated with the duration of ring use. The relationship between residual DPV levels and $AUC_{0\text{-tdays}}$ was more pronounced when the values from Group A and Group B were excluded. Values for the correlation coefficient ($r^2$) were 0.1 for both plasma and vaginal fluid, including the unreliable values, and 0.5 and 0.6 for plasma and vaginal fluid, respectively, after exclusion of Group A and Group B.[6]

**IPM 013** was a single center, Phase 1, randomized, double-blind, placebo-controlled trial conducted over three months in 48 sexually active women. Two groups of 24 women were randomly assigned (3:1) to DPV 25 mg VR or placebo VR. In Group A, the first VR was removed 28 days following enrollment, and a second ring inserted three days later on Day 31 and worn for 28 days. In Group B, the first ring was removed 35 days after enrollment (Day 35) and a second ring inserted three days later on Day 38 and worn for 21 days. A third ring was inserted 59 days after enrollment (Day 59) and worn for 24 hours. Quantifiable plasma (LLOQ = 3.00 pg/mL) and vaginal fluid (LLOQ = 0.4 ng) concentrations of DPV were observed within 4 hours after insertion of the first ring, indicating that DPV was readily released from the ring and absorbed into the surrounding tissue and into the bloodstream. Compared to vaginal fluids, systemic exposure to DPV in plasma was low. Plasma concentrations did not exceed 553 pg/mL, while the highest obtained individual vaginal fluid concentration was 171 µg/g. The lowest observed quantifiable vaginal fluid concentration between ring insertion and removal was 344 ng/g.[6]

In vaginal fluids, in the area of the ring, at the cervix and in the area of the introïtus, DPV concentrations increased rapidly and maximum concentrations were reached between Day 1 and Day 14 after ring insertion. Thereafter, vaginal fluid concentrations decreased steadily over the remainder of the 28-day or 35-day ring use period.[6]

Based on ratios of mean values of $C_{\text{prior to ring removal}}$ on Day 28 in Group A and Day 35 in Group B, vaginal fluid concentrations in the area of the ring and at the cervix were respectively 38% and 33% lower when the ring was worn for 35 days compared to 28 days. At the introïtus, the mean $C_{\text{prior to ring removal}}$ value was only 4% lower. These observations indicate that extending the period the ring was worn from 28 to 35 days

resulted in some reductions in vaginal fluid concentrations in the area of the ring (32.4 to 20.3 µg/g) and at the cervix (27.8 to 18.5 µg/g), but were similar at the introïtus (10.3 to 9.9 µg/g). These values remained at least 3000 times higher than the *in vitro* 99% inhibitory concentration (3.3 ng/mL) in cervical tissue. $C_{\text{prior to ring insertion}}$ values for the second ring were very low or below LLOQ. A vaginal lavage was performed prior to removal of the first ring, which likely removed much of the DPV from the vaginal area. As a result, $C_{\text{prior to ring removal}}$ was comparable between the first and the second rings in both groups. However, no vaginal lavage was performed prior to insertion of the third ring in Group B and this ring was inserted immediately after removal of the second ring. As a result, $AUC_{0\text{-}24h}$ in plasma and vaginal fluids was higher after insertion of the third ring as compared to the first ring; this was expected as the concentrations at the time the ring was replaced were well above LLOQ, as the second ring was only worn for 21 days. However, since $AUC_{0\text{-}24h}$ only covers a marginal part of the total exposure during one dosing interval (i.e. 28 days), no definite conclusions could be drawn regarding the degree of accumulation to steady state levels during continued treatment, when the ring is replaced every 28 days.[6]

**IPM 015** was a Phase 1/2, multicenter, randomized, double-blind, placebo-controlled trial conducted at 10 research centers in Kenya, Malawi, Tanzania and South Africa. The trial was performed in 280 sexually active women, to assess and compare the safety of Ring-004 and a placebo VR replaced every 28 days, for a total of 12 weeks. Eligible women were randomly assigned in a 1:1 ratio to one of two treatment groups. Rings containing DPV or placebo rings were inserted at 28-day intervals on the day of enrollment (Week 0), 4 weeks post-enrollment (Week 4), and 8 weeks post-enrollment (Week 8). During these visits the old ring was removed and replaced with a new ring. The third (last) ring was removed 12 weeks after enrollment (Week 12). Blood samples for determination of plasma concentrations of DPV were collected at Weeks 0, 4 and 12 just before removal of the ring. Residual DPV levels were measured in used or unused returned rings at Weeks 4, 8, and 12.[6]

Similar DPV plasma concentrations were observed at removal of the first VR at Week 4 (24 to 32 days after insertion), and at removal of the third VR at Week 12 (24 to 32 days after insertion). The mean plasma concentrations were 293.4 pg/mL and 238.9 pg/mL, respectively. The range of individual plasma DPV concentrations was similar at Week 4 and Week 12: at Week 4, the individual values ranged between 8.6 pg/mL and 708 pg/mL, and for Week 12 between below LLOQ (5 pg/mL) and 688 pg/mL. The inter-individual variability in DPV plasma levels was somewhat higher at Week 12 (CV of 61%) than Week 4 (CV of 46%). At Week 4, 50% of the plasma concentrations were between 209 pg/mL and 375 pg/mL (the lower and upper quartile, respectively). At Week 12, the corresponding values were 113 pg/mL and 329 pg/mL, respectively.[6]

In general, only a small amount of DPV was released from the VRs. The mean amounts remaining in the rings were similar for Weeks 4, 8 and 12, at 21.09 mg, 21.54 mg and 21.84 mg, respectively. The lower and upper quartiles were 20.4 and 21.9 mg (Week 4), 20.4 and 22.9 mg (Week 8), and 20.6 and 23.3 mg (Week 12).[6]

No clear relationship (neither linear nor exponential) was observed between the residual amount of DPV and corresponding plasma concentrations. Residual DPV amounts appeared to be negatively associated with plasma concentrations under 200 pg/mL, but appeared to be relatively constant for plasma concentrations above this value.

**IPM 024** was a Phase 1, randomized, double-blind, placebo-controlled trial, conducted at a single research center in Belgium in healthy, sexually abstinent women. Sixteen women were randomly assigned (1:1) to 25 mg DPV VR (Ring-004) or placebo VR for 28 consecutive days.[6]

Quantifiable plasma DPV concentrations (LLOQ = 3.00 pg/mL) were observed by 1.5 h post-ring insertion, and showed a gradual increase thereafter, reaching a mean $C_{max}$ of 355.0 pg/mL by Day 7 (median $t_{max}$). The mean plasma DPV concentration immediately before ring removal on Day 28 was 217.5 pg/mL. Individual plasma DPV concentrations did not exceed 1 ng/mL, and were well below the plasma concentration ($C_{max}$ = 2286 ng/mL) at the MTD for oral treatment.[6]

For DPV in vaginal fluids, quantifiable concentrations (LLOQ = 0.40 ng) were also observed by 1.5 h post-ring insertion, and the maximum concentrations were generally reached slightly earlier than in plasma. The highest concentrations were observed in the area near where the ring was placed (mean $C_{max}$: 79.9 µg/g; median $t_{max}$: Day 3), followed by the cervix (mean $C_{max}$:66.6 µg/g; median $t_{max}$: Day 4), and near the introïtus (mean $C_{max}$: 31.4 µg/g; median $t_{max}$: Day 14). The average concentration in the area of the ring was about 1.2 and 2.9 times higher than for the cervix and near the introïtus, respectively. At all three collection sites throughout the 28-day treatment period, DPV vaginal fluid concentrations were well above the *in vitro* $IC_{50}$ (0.3 ng/mL) for lab-adapted HIV-1 (LAI/IIIB) in T cells and the concentration at which greater than 99% inhibition of integrated provirus was observed (3.3 ng/mL) in cervical tissue following challenge with HIV-$1_{BaL}$. Prior to ring removal on Day 28, the mean concentrations ($C_{pre\text{-}ring\ removal}$) were 38.6 µg/g, 35.8 µg/g and 13.3 µg/g in the area of the ring, in the cervix and near the introïtus, respectively.[6]

By Day 56 (final visit), the plasma DPV concentrations of all participants but one were below the LLOQ (3.00 pg/mL). All DPV vaginal fluid concentrations were below the LLOQ (0.40 ng) by Day 56.[6]

It took several days after insertion for maximum concentrations to be achieved in vaginal fluid; this was also true in plasma. After ring removal, the terminal half-life of DPV in vaginal fluid was 12-16 hours on average; while the half-life in plasma was longer with a mean value of 67 hours.[6]

**MTN-013/IPM 026** was a Phase 1 safety and PK study of 48 healthy, HIV-uninfected, sexually abstinent, 18-40 year old women.[25] Participants were randomized to receive one of four study VRs (containing either 25 mg DPV, 100 mg maraviroc, 25 mg DPV + 100

mg maraviroc, or placebo) in a 1:1:1:1 ratio. The VR was to be used continuously for approximately 28 consecutive days. Safety assessments were conducted with special consideration for monitoring systemic toxicity and intensive PK assessments were conducted at multiple time points. MTN-013/IPM 026 was the first-in-human clinical trial that evaluated a VR containing maraviroc alone or in combination (DPV/maraviroc). The study design allowed safety comparisons of each product to a placebo and provided data regarding the absorption and distribution of the drug(s) administered. All four study VRs were safe and well tolerated. DPV was consistently detected in plasma, cervicovaginal fluid (CVF) and cervical tissue; maraviroc was consistently detected only in CVF. DPV levels in tissue were about 10,000-fold higher than in plasma and 10-fold lower than in CVF for both DPV only and combination VR study arms. DPV, but not maraviroc, demonstrated concentration-dependent inhibition of HIV-1 infection in cervical tissue.[25] Analysis of cervical concentrations demonstrated 100 ng/mL of DPV was need to provide a 50% reduction in HIV-1 replication.[26]

**Dapivirine VRs: DPV 200 mg VR (Ring-001)**

The PK profile of a 200 mg DPV ring with a reservoir configuration, Ring-001, was investigated in a Phase 1, crossover, open-label trial in 12 healthy, sexually abstinent, HIV-negative women (IPM 001). Each woman used a placebo silicone elastomer VR for 7 days followed by 7 days of use of a VR containing 200 mg DPV. Only limited data are available. Plasma concentrations were measured from 4 hours through 7 days post-insertion of the VR, and showed that plasma levels of DPV were consistently below the limit of quantification (LLOQ = < 50 pg/mL).[6, 23]

Samples of vaginal fluids from the introïtus, cervix, and ring area were collected at 4 hours, 24 hours, and 7 days after insertion of the VR. At 4 hours and 24 hours post-insertion, mean DPV concentrations in vaginal fluids were higher in the ring area (38.7; 82.0 ng/strip) than at the introïtus (2.6; 6.9 ng/strip) or cervix (17.0; 25.7 ng/strip). At 7 days post-insertion, mean concentrations at the introïtus, cervix, and ring area were 16.6 ng/strip, 18.3 ng/strip and 30.8 ng/strip, respectively. Tissue biopsies of the vagina (introïtus and ring area) and cervix were collected immediately following removal of the VR, 7 days after insertion. Mean DPV concentrations were higher in the ring area (0.7028 µg/g) than in the introïtus (0.2785 µg/g) or cervix (0.2893 µg/g). The lowest observed concentration of DPV in any tissue sample (0.028 µg/g, at the introïtus) was over 30-fold greater than the reported $EC_{90}$ for DPV in vitro. DPV levels in vaginal fluids were between 10 and 28 times higher, and in cervical tissue about five times higher, for Ring-004 than Ring-001.[6, 23]

### 2.4.3 Safety of Dapivirine

***Oral dapivirine***:
In a series of 11 oral DPV clinical trials, 211 participants were exposed to oral doses of DPV ranging from 50 mg to 1000 mg daily. The MTD for a single dose was 350 mg and for multiple doses 300 mg b.i.d. No trials were stopped for safety reasons, and no deaths occurred during these trials. Treatment emergent adverse event (TEAE) reported in more than 2% of participants included headache, dizziness, nausea, diarrhea, fatigue, tremor, somnolence, flatulence and vomiting. Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) up to grade 3 in intensity were observed but these increases were generally transient and did not result in permanent liver impairment. One HIV-infected participant was withdrawn from the trial due to elevated AST and ALT, which were deemed to be caused by an acute concomitant hepatitis C infection. This event was the only serious adverse event (SAE) which led to withdrawal from the trial across all trials with oral DPV.[6]

***Vaginally administered dapivirine:***
Considering the lack of significant local and systemic toxicities observed in ongoing and completed trials with vaginally administered DPV and comparing systemic exposure from orally administered to vaginally administered DPV, a wide safety margin exists for daily dosing of vaginally administered DPV.[23]

**Gel Studies:** In a series of eight Phase 1/2 DPV vaginal gel clinical trials that assessed PK, safety and acceptability endpoints, a total of 774 participants were enrolled of whom 491 participants used DPV vaginal gels of various concentrations. The trials were conducted in the United States, Belgium, Malawi, Kenya, Rwanda, South Africa, and Tanzania. Maximum exposure (days) to the gels ranged from 7 days to 84 days during these trials. The results of clinical trials with DPV gels showed that they were generally safe and well tolerated. Six participants required permanent discontinuation of the IP due to non- serious adverse events (AEs) which were regarded by the Investigator as at least possibly related to product use. The events included in the DPV treatment arm, a Grade 1 hypersensitivity (reported as allergic response with symptoms and signs that included vaginal burning, itching and erythema), Grade 1 worsening of a cervicovaginal human papilloma virus (HPV) infection, Grade 2 vulvar irritation along with vaginal pruritus in the same participant), and Grade 1 intermenstrual bleeding.[10]

Across all completed clinical gel trials, the most commonly reported TEAEs (documented in at least 5% of women who used DPV gel) were metrorrhagia, headache, bacterial vaginitis, and vaginal candidiasis.[10]

**DPV VRs (Phase 1/2 studies):** Across all completed clinical trials with DPV VRs (Rings 001, 002, 003 and 004), the DPV VR was generally safe and well tolerated. One participant assigned to DPV Ring-004 required permanent discontinuation of the IP due to a non-serious AE (Grade 2 generalized pruritus) which was regarded by the Investigator as possibly related to product use. Three Grade 3 SAEs (thoracic vertebral

fractures, fracture of the right acetabulum and tonsillitis) were reported for three participants who used the DPV VR-004; all three events were regarded by the Investigator as unrelated to ring use.[6]

Six SAEs have been reported in participants using the placebo ring, including one participant who experienced two SAEs: Grade 3 (severe) bacterial gastroenteritis and Grade 4 (life-threatening) pyrexia. The participant was discontinued from the trial (IPM 024). The SAEs were assessed by the Investigator as unrelated to IP. Other reported SAEs in participants using placebo rings included a Grade 4 hemopneumothorax (following physical assault) which ultimately led to the participant's death, a Grade 3 event of bronchiectasis, a Grade 3 peritonsillar abscess, and a Grade 3 psychiatric disorder (suicide attempt). None of the reported SAEs in placebo ring users were regarded by the Investigator as related to ring use.[6]

Across all completed DPV Ring-004 clinical trials (IPM 034, IPM 028, IPM 024, IPM 015, and IPM 013), the cumulative incidence of TEAEs was generally similar (or lower in some cases) in the DPV ring compared to the placebo ring groups. TEAEs that occurred in ≥ 5% of DPV Ring-004 users were metrorrhagia, headache, gynecological chlamydia (CT) infection, vaginal candidiasis, urinary tract infection (UTI), vaginal discharge, upper respiratory tract infection, lower abdominal pain, nasopharyngitis, and nausea. Metrorrhagia (29.7% vs. 24.4%), headache (15.1% vs. 11.9%) and vulvovaginal discomfort (2.7 vs. 1.3%) were reported more frequently in users of the DPV VR than the placebo ring respectively.[6]

**DPV VRs: Phase 3 studies**

**IPM 027 (The Ring Study):** The rate of AEs, including product-related AEs, urogenital AEs and deaths, was similar between the DPV and placebo groups. Although the rate of SAEs was statistically significantly higher in the DPV VR group than the placebo group (2.9% vs. 0.9%, p=0.008), no patterns were identified to indicate clinical relevance. The cumulative incidence of TEAEs was similar in DPV VR users (1142/1306; 87.4%) and placebo VR users (559/652; 85.7%) (Table 4). Gynecological CT infection was reported most frequently, with a similar incidence observed in the DPV and placebo VR groups. All cases were moderate (Grade 2) in severity. Apart from gynecological CT infection, the TEAEs reported most frequently (by at least 10% of participants using DPV VRs) were metrorrhagia, female genital infection, genitourinary tract gonococcal infection, upper respiratory tract infection, trichomoniasis, UTI, and vulvovaginal candidiasis.[6, 14]

**Table 4: Incidence of Treatment-Emergent Adverse Events Reported Most Frequently (Incidence ≥ 10% in Participants Using DPV VRs), Regardless of Causality in IPM 027**

| MedDRA SOC/Preferred Term (MedDRA v 15.0) | Dapivirine (N=1307) | Placebo (N=652) |
|---|---|---|
| | n (%) | n (%) |
| Participants with at least one TEAE | 1142 (87.4%) | 559 (85.7%) |
| INFECTIONS AND INFESTATIONS | | |

| MedDRA SOC/Preferred Term (MedDRA v 15.0) | Dapivirine (N=1307) | Placebo (N=652) |
|---|---|---|
| Gynaecological chlamydia infection | 400 (30.6%) | 205 (31.4%) |
| Genital infection female* | 287 (22.0%) | 115 (17.6%) |
| Genitourinary tract gonococcal infection | 234 (17.9%) | 106 (16.3%) |
| Upper respiratory tract infection | 225 (17.2%) | 109 (16.7%) |
| Trichomoniasis | 217 (16.6%) | 95 (14.6%) |
| Urinary tract infection | 180 (13.8%) | 97 (14.9%) |
| Vulvovaginal candidiasis | 165 (12.6%) | 76 (11.7%) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | | |
| Metrorrhagia | 335 (25.7%) | 182 (27.9%) |
| * This term described events where there was a clinical suspicion of genital infection and syndromic treatment given but no etiology was confirmed. | | |

SAEs were reported by 44 participants (38 [2.9%] participants in the DPV VR group and six [0.9%] participants in the placebo VR group). The events varied in intensity from Grade 1 (mild) to Grade 5 (death); none were considered by the investigator as related to the VRs. Two participants in the DPV VR group died due to multiple injuries sustained in a motor vehicle accident and a gunshot wound respectively, and one placebo VR user died as a result of circulatory collapse during an episode of substance abuse.[6]

Product-related events (as assessed by the investigator) were reported for five (0.4%) participants in the DPV VR group and included metrorrhagia (reported for two participants), pelvic discomfort, pelvic pain, and suprapubic pain, each reported for one participant. Three placebo VR users experienced a product-related event that included pelvic discomfort, menometrorrhagia and application site pain. All product-related events in both groups were assessed by the investigator as mild in severity.[6]

One participant assigned to the DPV Ring-004 discontinued the trial early due to a Grade 2 non-product related AE (cervical dysplasia) which required further evaluation and treatment.[6]

**MTN-020 (ASPIRE):** No statistically significant differences were identified between the DPV VR and placebo VR arms in frequency of the primary safety endpoint (defined as the incidence of any SAE, any Grade 3 or 4 AE, and any Grade 2 AE that was assessed by the investigator as being related to the IP) or in other AEs commonly detected in the trial population (Table 5). The most commonly occurring AE was metrorrhagia. Other frequently reported AEs (occurring in ≥ 10% of trial participants) included genitourinary CT infection, menorrhagia, UTI, menometrorrhagia, vulvovaginal candidiasis, bacterial vaginosis (BV), vaginal discharge, upper respiratory tract infection, increased AST and ALT, abnormal weight loss, genitourinary tract gonococcal infection, trichomonal

vulvovaginitis, vulvovaginal pruritus, pelvic pain, decreased hemoglobin, and decreased neutrophil count.[6, 13]

**Table 5: Adverse Events in MTN-020 (ASPIRE)**

| | Placebo VR (N=1316) | Dapivirine VR (N=1313) |
|---|---|---|
| | n (%) | n (%) |
| Primary safety endpoint* | 186 (14%) | 180 (14%) |
| Any SAE | 48 (4%) | 52 (4%) |
| Death | 3 (<1%) | 4 (<1%) |
| Any Grade 4 AE | 23 (2%) | 22 (2%) |
| Any Grade 3 AE | 162 (12%) | 151 (12%) |
| Any Grade 2 AE assessed as related | 9 (1%) | 7 (1%) |

* The primary safety endpoint of the trial was defined as any SAE, any Grade 3 or Grade 4 AEs, and any Grade 2 AE assessed by the investigator as related to the IP. Overall chi-squared P-value = 0.80.

SAEs were reported by 100 participants (52 [4.0%] participants in the DPV VR group and 48 [3.6%] participants in the placebo VR group). The events varied in intensity from Grade 1 (mild) to Grade 5 (death); none were considered by the investigator as related to the IP. Four deaths were reported in the DPV VR group: two participants died from fatal stab wounds, one participant died from an abdominal injury due to a physical assault, and one participant died from dyspnea considered secondary to a pulmonary embolism. Three participants in the placebo VR group died due to a fatal stab wound, gastrointestinal tuberculosis, and pulmonary tuberculosis, respectively.[6]

Grade 2 (moderate) product-related events (as assessed by the investigator) were reported for seven (0.5%) participants in the DPV VR group and included pelvic pain (reported for two participants), cervix erythema, cervix edema, cervicitis, UTI, urinary incontinence, dyspareunia, and headache, each reported for one participant. Nine (0.7%) placebo VR users experienced a Grade 2 product-related event that included application site pain (reported for two participants), pelvic inflammatory disease (PID), cervicitis, UTI, decreased neutrophil count, abnormal weight loss, dysmenorrhea, and pelvic pain, each reported for one participant. No Grade 3 (serious) or Grade 4 (potentially life threatening) product-related events were reported in the trial.[6]

***Safety of extended continuous use of a single DPV VR (Ring-004):***

In extended use of a single 25 mg DPV Ring-004 (IPM 034) for a period of up to 84 days, the VR was considered generally safe and well tolerated. Forty HIV-negative female participants were administered a single VR in this safety and PK study and instructed to wear it continuously for different lengths of time (7, 14, 28, 56, or 84 days). Eligible participants were enrolled into five groups of eight women each. There was no placebo arm. No non-serious AEs led to the investigator taking action to permanently discontinue use of the DPV VR in any participant. The vast majority of AEs were of mild or moderate intensity. Apart from metrorrhagia, the TEAEs reported most frequently (by at least 5.0% of participants using the DPV rings) were nasopharyngitis, lower abdominal pain, headache, vaginal discharge, oropharyngeal pain, nausea, and procedural pain. The only

AEs reported in the Reproductive and Breast Disorders System Order Class were grade 1 (mild) vaginal discharge and metrorrhagia.[6]

**Efficacy of Dapivirine VR for Prevention of HIV**

The safety and efficacy of the VR matrix containing DPV 25 mg (Ring 004) replaced monthly were recently tested in two randomized, double-blind, placebo-controlled Phase 3 trials: MTN-020 (ASPIRE) and IPM 027 (The Ring Study). Both trials demonstrated that the VR was safe and was effective for prevention of HIV-1 acquisition.[13, 14] In IPM 027, a total of 133 post-randomization HIV-1 infections occurred: 77 among women assigned to the DPV VR (incidence 4.08 per 100 person-years) and 56 among women assigned to placebo VR (incidence 6.10 per 100 person-years).[14] The DPV VR reduced the risk of HIV-1 infection by 30.7% (95% CI: 0.90-51.5%; p=0.0401) relative to placebo VR. A 37.5% (95% CI: 3.5-59.5%) reduction in HIV-1 infection was observed in a subgroup analysis of women older than 21 years.[14]

In MTN-020, a total of 168 HIV-1 infections occurred: 71 among those assigned the DPV VR and 97 among those assigned the placebo VR (incidence 3.3 and 4.5 per 100 person-years, respectively).[13] The DPV VR resulted in a 27% (95% CI: 1-46%, p=0.05) relative reduction in HIV-1 incidence overall, a 37% (95% CI: 12-56%, p=0.007) reduction in an analysis defined early in the study, excluding data from two study sites with lower retention and adherence, and a 56% (95% CI: 31-71%, p<0.001) reduction in a post-hoc analysis among women older than 21 years of age.[13] In pre-defined as-randomized subgroup analyses, HIV protection differed significantly by age, with a 61% reduced risk of HIV for women ≥ 25 years [CI: 32%, 77%)] p<0.001, and 10% reduced risk for women < 25 years (CI: -41%, 43%) p=0.64. A post-hoc analysis was conducted to further explore this result, which indicated a 56% (95% CI: 31-71%, p<0.001) reduction among women older than 21 years of age. HIV-1 protection was not observed for women aged 18-21, and objective markers of adherence were lower in this subgroup compared to women older than 21.[13] Across multiple analyses, there was a statistically significant relationship between VR use and HIV protection; these analyses provide evidence suggesting a dose-response relationship between VR use and HIV acquisition. The ASPIRE results suggest VR use is associated with at least 56% and potentially >65% protection when used consistently.[27] Finally, among those acquiring HIV-1, the detection of NNRTI mutations did not differ by study arm (8/68 [12%] assigned DPV and 10/96 [10%] assigned placebo, p=0.80).[13] The frequency of ARV resistance was also similar between study arms.[13]

## 2.5 Study Hypotheses and Rationale for Study Design

### 2.5.1 Study Design

The design of MTN-036/IPM 047, a clinical study of DPV VRs in women, will provide data to compare the PK and safety profile of two extended duration DPV VRs (100 and 200 mg) to the current monthly 25 mg DPV VR shown to be safe and effective in the Phase 3 studies ASPIRE and The Ring Study. A single 100 or 200 mg VR will be used continuously for approximately 13 weeks, while the 25 mg VR will be replaced every 4 weeks for 8

weeks and then worn for an additional 5 weeks for approximately 13 weeks (and 3 rings) in total. Participants randomized to the extended use VRs (100 mg and 200 mg) will not be told their group assignment to minimize potential bias in self-reports. It is important to reiterate that the anticipated drug exposure due to the release from the 100 and 200 mg DPV VR is anticipated to fall within pre-established preclinical and clinical safety margins for which vaginally administered data exist.[28]

MTN-036/IPM 047 will evaluate DPV levels in plasma, CVF and cervical tissue during 13 weeks of continuous use of a single ring containing 100 mg or 200 mg DPV, and multiple (n=3) 25 mg VRs replaced every 4 weeks for 8 weeks and then worn for an additional 5 weeks for a total of 13 weeks. PK data will help determine the concentration-time profiles using pooled data across all participants. The study design includes frequent collection of corresponding blood and vaginal fluid samples following the insertion of a DPV VR to allow for the detection of burst release from the ring. PK parameters of DPV will be calculated for blood plasma, CVF, and cervical tissue.

### 2.5.2 Study Hypotheses

- Plasma, CVF, and cervical tissue DPV levels will be measureable in all participants
- Continuous exposure to DPV due to sustained release from the 100 mg and 200 mg VRs for 13 weeks will be safe
- Dose-proportionality will be demonstrated in tissue and systemic PK

# 3 OBJECTIVES

## 3.1 Primary Objectives

**Pharmacokinetics**

- To compare the local and systemic pharmacokinetics (PK) of two extended duration DPV VRs (100 mg and 200 mg) when used continuously for 13 weeks to the current 25 mg DPV VR when replaced every 4 weeks for 8 weeks and then worn for an additional 5 weeks for a total of 13 weeks

**Safety**

- To compare the safety of the two extended duration DPV VRs (100 mg and 200 mg) to the current 25 mg DPV VR when used for 13 weeks

## 3.2 Secondary Objectives

**Adherence**

- To evaluate participant adherence to the three DPV VRs when used for 13 weeks

**Acceptability**

- To compare overall acceptability of the two extended duration DPV VRs (100 mg and 200 mg) to the current 25 mg DPV VR

### 3.3 Exploratory Objectives

**Vaginal Microenvironment**

- To describe the genital microenvironment in HIV-uninfected women and those assigned female sex at birth using a DPV VR for 13 weeks

**Pharmacokinetics**

- To compare the rectal compartment PK of the two extended duration DPV VRs (100mg and 200 mg) when used continuously for 13 weeks to the current 25 mg DPV VR

**Adherence**

- To evaluate markers of ring use for the three DPV VRs

**Acceptability**

- To evaluate components of acceptability of ring use for the three DPV VRs

# 4 STUDY DESIGN

### 4.1 Identification of Study Design

MTN-036/IPM 047 is a Phase 1, three-arm, multi-site, randomized trial of three silicone elastomer VRs containing the active ingredient DPV at three loading levels. Healthy, HIV-uninfected women and those assigned female sex at birth age 18-45 (inclusive) will use one of three DPV VRs: the 100 and 200 mg study VRs are inserted once and used continuously for approximately 13 weeks; the 25 mg study VR is replaced every 4 weeks for 8 weeks, then worn for an additional 5 weeks for approximately 13 weeks in total. Participants randomized to the 100 mg or 200 mg study VRs will not be told their group assignment.

### 4.2 Primary Endpoints

**Pharmacokinetics**

- DPV concentrations in plasma
- DPV concentrations in cervicovaginal fluid
- DPV concentrations in cervical tissue

**Safety**

- Proportions of participants with Grade 2 or higher genitourinary adverse events as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, March 2017, and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])
- Proportions of participants with Grade 3 or higher adverse events as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, March 2017

## 4.3 Secondary Endpoints

**Adherence**

- Frequency of study VR removal/expulsions (voluntary and involuntary) and duration without VR in vagina (by self-report)
- VR use initiation and persistence (whether the VR is in place when participants come to the clinic for their study visits)

**Acceptability**

- Degree to which study participants liked or disliked using the three DPV VRs (by self-report)

## 4.4 Exploratory Endpoints

**Vaginal Microenvironment**

- Changes in microbiota and biomarkers during DPV VR use

**Pharmacokinetics**

- DPV concentrations in rectal fluid

**Adherence**

- Plasma DPV levels
- Residual DPV levels in returned VRs

**Acceptability**

- Self-reported attitudes about VR attributes, including dosing regimen, and willingness to use the VR in the future
- Interest/preference in a single vs. dual-purpose indication
- Proportion of participants who find the study VRs to be at least as acceptable as other HIV prevention methods

### 4.5 Description of Study Population

The study population will be healthy, HIV-uninfected women and those assigned female sex at birth who meet the criteria outlined in Sections 5.2 and 5.3.

### 4.6 Time to Complete Accrual

Accrual is expected to be complete in approximately 6-9 months.

### 4.7 Study Groups

Approximately 48 participants will be randomized in a 1:1:1 ratio to one of the following study groups:

- 25 mg DPV VR
- 100 mg DPV VR
- 200 mg DPV VR

### 4.8 Expected Duration of Participation

The expected trial duration for each enrolled participant is approximately 94 days.

### 4.9 Sites

Sites selected by the MTN Executive Committee.

# 5 STUDY POPULATION

### 5.1 Selection of the Study Population

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

#### 5.1.1 Recruitment

Participants will be recruited from a variety of sources across sites, including family planning and gynecological offices, colleges and universities, online websites, faith communities, as well as community-based locations such as community-based organizations and street-based outreach. In addition, participants may be referred to the study from other local research projects and other health and social service providers. Recruitment materials and the site recruitment plan will be approved by site Institutional Review Boards (IRBs) prior to use. Advice regarding these materials will be sought from site community representatives before they are submitted to the IRB for review.

### 5.1.2 Retention

Once a participant is enrolled/randomized in MTN-036/IPM 047, 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 at each site. All study sites will be responsible for developing and implementing local standard operating procedure (SOPs) to achieve this. Engaging peer educators/advocates or organizations in retention messaging, etc. may be used to facilitate MTN-036/IPM 047 retention.

## 5.2 Inclusion Criteria

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

1) Assigned female sex at birth

   *Note: Participants who are female at birth, who now identify as male, will not be excluded so long as they are not on female-to-male transition therapy.*

2) Age 18 through 45 years (inclusive) at Screening, verified per site SOPs

3) Able and willing to provide written informed consent to be screened for and enrolled in MTN-036/IPM 047

4) Able and willing to provide adequate locator information, as defined in site SOPs

5) Able to communicate in spoken and written English

6) Available for all visits and able and willing to comply with all study procedural requirements

7) Willing to comply with abstinence and other protocol requirements as outlined in Sections 6.6 and 6.7

8) Willing to use male condoms for penile-vaginal intercourse (PVI) and penile-rectal intercourse for the duration of study participation

9) Per participant report, using an effective method of contraception for at least 30 days (inclusive) prior to Enrollment, and intending to continue use of an effective method for the duration of study participation; effective methods include:
   a) hormonal methods (except contraceptive ring)
   b) intrauterine device (IUD)
   c) sterilization (of participant or partner, as defined in site SOPs)
   d) having sex exclusively with cis-women
   e) abstinence from PVI for 90 days prior to Enrollment, and intending to remain abstinent from PVI for the duration of study participation

10) In general good health as determined by the Investigator of Record (IoR)/designee at Screening and Enrollment

11) HIV-uninfected based on testing performed at Screening and Enrollment (per protocol algorithm in Appendix II)

12) Per participant report at Screening, regular menstrual cycles with at least 21 days between menses

    *Note: This criterion is not applicable to participants who report using a progestin-only method of contraception at Screening (e.g., Depo-Provera or levonorgestrel-releasing IUD) nor to participants using continuous combination oral contraceptive pills, as the absence of regular menstrual cycles is an expected, normal consequence in this context.*

13) Per participant report at Screening and Enrollment, states a willingness to refrain from inserting any non-study vaginal products or objects into the vagina including, but not limited to spermicides, female condoms, diaphragms, intravaginal rings, vaginal medications, menstrual cups, cervical caps, douches, lubricants, and sex toys (vibrators, dildos, etc.) for the 24 hours preceding the Enrollment Visit and for the duration of study participation.

    *Note: Use of tampons is permitted except for 24 hours prior to clinic visits in which CVF samples are scheduled to be collected.*

14) Participants 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 (Dated November 2007) to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1, March 2017, or satisfactory evaluation with no treatment required of Grade 1 or higher Pap result

15) At Screening and Enrollment, agrees not to participate in other research studies involving drugs, medical devices, vaginal products or vaccines after the Screening Visit and for the duration of study participation

### 5.3 Exclusion Criteria

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

1) Pregnant at Screening or Enrollment or plans to become pregnant during the study period

    *Note: A documented negative pregnancy test performed by study staff is required for inclusion; however a self-reported pregnancy is adequate for exclusion from the study.*

2) Diagnosed with a UTI or reproductive tract infection (RTI) at Screening or Enrollment

*Otherwise eligible participants diagnosed with UTI/RTI during screening will be offered treatment. If treatment is complete and symptoms have resolved within the 45 day screening window, eligible participants may be enrolled.*

3) Diagnosed with an acute STI requiring treatment per current Centers for Disease Control and Prevention (CDC) guidelines (http://www.cdc.gov/std/treatment/) at Screening or Enrollment such as gonorrhea (GC), CT, trichomonas, PID, and/or syphilis

*Note: Genital warts requiring treatment and frequent recurrence of herpes simplex virus (HSV) are considered exclusionary; however, infrequent HSV outbreaks are not. Genital warts requiring treatment are defined as those that cause undue burden or discomfort to the participant, including bulky size, unacceptable appearance, or physical discomfort. See MTN-036/IPM 047 Study-Specific Procedures (SSP) Manual for additional information.*

4) Has a clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff) at Screening or Enrollment, as per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, March 2017, and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])

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

*Note: Otherwise eligible participants with exclusionary pelvic exam findings may be enrolled/randomized after the findings have improved to a non-exclusionary severity grading or resolved within 45 days of providing informed consent for screening.*

5) Participant report and/or clinical evidence of any of the following:

a) Known adverse reaction to any of the study products (ever)
b) Chronic and/or recurrent vaginal candidiasis
c) Non-therapeutic injection drug use in the 12 months prior to Enrollment
d) Last pregnancy outcome less than 90 days prior to Enrollment
e) Gynecologic or genital procedure (e.g., tubal ligation, dilation and curettage, piercing) 45 days or less prior to Enrollment

*Note: Colposcopy and cervical biopsies for evaluation of an abnormal Pap test as well as IUD insertion/removal are not exclusionary.*

f) Currently breastfeeding or planning to breastfeed during the study period
g) Participation in any other research study involving drugs, medical devices, vaginal products or vaccines, in the 60 days prior to Enrollment

6) Use of pre-exposure prophylaxis (PrEP) for HIV prevention and/or post-exposure prophylaxis (PEP) for potential HIV exposure within the 3 months prior to Enrollment, and/or anticipated use and/or unwillingness to abstain from PrEP during trial participation

7) Has any of the following Grade 1 or higher laboratory abnormalities at Screening Visit:
   a) AST or ALT*
   b) Hemoglobin*

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

8) Has any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate the interpretation of study outcome data, or otherwise interfere with achieving the study objectives including any significant uncontrolled active or chronic medical condition.

*DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, March 2017, and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])

## 5.4 Co-enrollment Guidelines

As indicated in Sections 5.2 and 5.3, participants must not take part in other research studies involving drugs, medical devices, vaginal products or vaccines after the Screening Visit and while taking part in MTN-036/IPM 047 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 while on study product will be offered enrollment in MTN-016 (provided their study site is taking part in MTN-016)

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-036/IPM 047, the IoR/designee will consult the PSRT regarding ongoing product use and other potential safety considerations associated with co-enrollment.

# 6 STUDY PRODUCT

## 6.1 Regimen

Each participant will be randomized to one of three DPV VRs:

**Table 6: Study Regimen**

| Group | N | Ring Description |
|---|---|---|
| A | 16 | DPV VR containing 25 mg DPV |
| B | 16 | DPV VR containing 100 mg of DPV |
| C | 16 | DPV VR containing 200 mg of DPV |

Each participant will receive a VR containing either 25 mg DPV, 100 mg DPV or 200 mg DPV. Participants will be randomized in a 1:1:1 ratio. A new 25 mg VR is inserted approximately every 4 weeks for the first 8 weeks, and the third VR inserted will be worn for approximately 5 weeks for a total of 13 weeks of product use (3 VRs total). The VRs containing 100 mg or 200 mg DPV are inserted once and used continuously for approximately 13 weeks.

The ring will be removed by the participant (or clinician/designee, if necessary) at monthly visits for participants receiving the 25 mg VR, and at the product use end visit (PUEV/Early Termination Visit) for all participants. Participants will be followed for approximately 1-3 days following final VR removal.

## 6.2 Administration

At the Enrollment Visit the VR will be inserted by the participant (or clinician/designee, if necessary). Participants will be given detailed instructions in the clinic on proper VR insertion and removal procedures. Details on administration (ring insertion, removal, procedures in the event of expulsion) will be provided in the MTN-036/IPM 047 SSP Manual.

## 6.3 Study Product Formulation and Storage

The 25 mg rings are designed to provide sustained release of drug over a minimum period of one month. The 100 mg and 200 mg rings are designed to provide sustained release of drug over a 90-day period +/-3 days.

### 6.3.1 Dapivirine 25 mg VR (Polymer 4870, IPM Ring-004)

The comparator VR is an off-white, flexible ring containing 25 mg of DPV 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 DPV 25 mg VR is designed to provide sustained release of drug over a minimum period of one month.

The DPV 25 mg VR optimally should be stored in the site pharmacy at 20°C to 25°C, with allowable excursions between 15°C to 30°C.

### 6.3.2 Dapivirine 100 mg VR (Polymer 4870, IPM Ring-008) and 200 mg VR (Polymer 4870, IPM Ring-006)

The 100mg and 200 mg DPV VRs are flexible rings containing either 100 mg or 200 mg of DPV dispersed in a platinum-cured silicone matrix. The dimensions of the rings are 56 mm and 7.7 mm, outer diameter and cross-sectional diameter, respectively. The 100 mg and 200 mg DPV VRs are designed to provide sustained release of DPV over a minimum of 3 months.

The 100 mg and 200 mg DPV VRs optimally should be stored in the site pharmacy at 20°C to 25°C, with allowable excursions between 15°C to 30°C.

## 6.4 Supply and Accountability

### 6.4.1 Supply

IPM (Silver Spring, MD) will oversee the manufacture of all of the study VRs and analysis/release of the rings under Good Manufacturing Practices (GMP).

### 6.4.2 VR Dispensing

Study VRs will be dispensed to clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. Participants in the 25 mg DPV VR arm will receive one VR at the enrollment visit (Visit 2), one VR at Visit 8, and one VR at Visit 9. These participants will use a 25 mg DPV VR for a total of approximately 13 weeks. Participants receiving the 100 mg or 200 mg DPV VR will receive one VR at the enrollment visit (Visit 2) and will use the VR for approximately 13 weeks. Provisions for the dispensation of additional VRs will be at the discretion of the IoR and in consultation with the PSRT as needed.

### 6.4.3 Accountability

Each Clinical Research Site (CRS) Pharmacist of Record (PoR) is required to maintain a complete record of all VRs received and subsequently dispensed. All unused study products must be returned to the MTN Pharmacist after the study is completed or terminated unless otherwise instructed by the MTN Pharmacist. The procedures to be followed are provided in the MTN-036/IPM 047 Pharmacy Study Product Management Procedures Manual.

All VRs provided to a participant must be documented by the clinic staff when they are returned. This includes VR(s) brought back to the clinic by the participant and any ring removed at the clinic visit. Any VRs not returned must also be documented by the clinic.

### 6.4.4 Retrieval of Used Study Product

Study participants receiving the 25 mg VR will be instructed to return to the clinic for VR removal approximately every 4-5 weeks until study completion. All participants will be instructed to return for VR removal at the PUEV/Early Termination Visit. In the event that the participant has removed the VR and it is not returned at the PUEV/Early Termination Visit, site staff members will make every effort to encourage participants to return the VR as soon as possible (optimally within 5 working days). Attempts by study staff to retrieve the VR from the participant must be documented.

When product use is permanently discontinued for HIV infection or pregnancy, the VR must be retrieved (optimally within 24 hours of site awareness) and returned to the clinic (see Table 7 below). Additional VR retrieval specifications in response to discontinuations for other reasons, or IoR discretion, can be found in Table 7. Study product retrieval may occur either by the participant returning the VR to study staff within the specified timeframe or attempts should be made by study staff to contact the participant and retrieve the VR as soon as possible. If the VR is not returned within the time frames outlined below, the MTN-036/IPM 047 PSRT must be notified.

**Table 7: Retrieval of VR**

| Reason for Ring Removal | Timeframe for Study Product Retrieval |
|---|---|
| Permanent discontinuation or temporary hold due to potential HIV infection or pregnancy | Within 24 hours |
| Permanent discontinuation for any other reason or IoR discretion | Within 5 working days |
| Temporary hold for reasons with expected duration of greater than 7 days | Within 7 working days |

In the event that there is a product hold, expulsion (i.e., ring removed and cannot be reinserted) or an extended period of time that the ring is removed, the MTN-036/IPM 047 PSRT should be notified. The PSRT will evaluate each reported event to determine if the ring should be reinserted, if a new ring should be dispensed, or if the participant should discontinue product use. See Section 9 for additional information related to study product holds.

## 6.5 Concomitant Medications

Enrolled study participants may use concomitant medications during study participation with the exception of medications and products noted as prohibited in Sections 6.6 and 6.7. All concomitant medication use reported throughout the course of the study will be entered on case report forms (CRFs) 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 Prohibited Medications

The use of PEP and PrEP are prohibited during study participation. Use of anticoagulants or blood-thinners (such as heparin, Lovenox®, warfarin, and Plavix® [clopidogrel bisulfate]) is prohibited during study participation. See Section 9.3 for additional information.

Participants are asked to abstain from using aspirin (greater than 81 mg) within 72 hours prior to and following a cervical biopsy collection visit (Visits 8 and 10). Should a participant report taking any of the medications noted above, which may increase risk of bleeding, or engaging in receptive vaginal sexual activities the visit should be rescheduled within the visit window, if possible. If it is determined that rescheduling the visit within the window is not possible, the visit may proceed at IoR discretion after proper participant counseling has occurred.

### 6.7 Intravaginal and Rectal Medications, Products and Practices

All participants will be counseled to avoid the use of non-study intravaginal and rectal products and other devices. These include, but are not limited to, spermicides, female condoms, diaphragms, non-study intravaginal rings, vaginal medications, menstrual cups, cervical caps, douches, lubricants, and sex toys (e.g., vibrators, dildos, etc.) for the 24 hours preceding the Enrollment Visit and for the duration of study participation. Use of these products will be captured in the study database. Participants who report use of these products during study product use will be counseled regarding the use of alternative methods and study staff should reference Section 9.3 for permanent discontinuation guidelines.

Participants are asked to abstain from receptive vaginal and anal sexual activities for 72 hours prior to each clinic visit and to abstain from from vaginal sexual activities for 72 hours after biopsy collection.

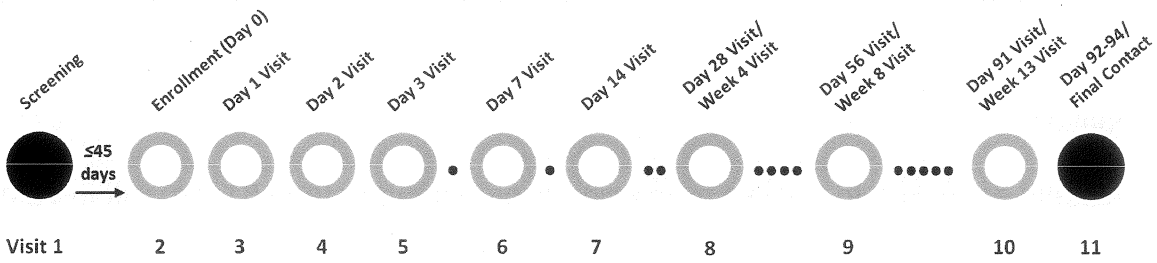
While tampon use is not prohibited, participants will be instructed to restrict use for 24 hours prior to any clinic visit in which CVF samples are collected.

All participants will be offered male condoms. The condoms will be made available in the clinic and will be dispensed by the clinic staff.

# 7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is provided in Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites as well as to specify the visit windows are provided in the MTN-036/IPM 047 SSP Manual available at www.mtnstopshiv.org.

**Figure 4: Study Visit Schedule**




## 7.1 Pre-screening

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

## 7.2 Screening Visit - Visit 1

A Screening Visit may take place up to 45 days prior to the Enrollment Visit (Day 0). Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed participant consent for Screening/Enrollment will be obtained at the Screening Visit before any screening procedures are initiated. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined.

*NOTE: Participants who fail their first screening attempt may be re-screened one time.*

**Table 8: Screening Visit - Visit 1**

| Screening Visit - Visit 1 | | |
|---|---|---|
| **Component** | | **Procedure/Analysis** |
| **Administrative and Regulatory** | | • Obtain written informed consent<br>• Assign a unique Participant Identification (PTID) number<br>• Assess eligibility<br>• Collect demographic and background information<br>• Collect locator information<br>• Provide reimbursement<br>• Schedule next visit/contact* |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling<br>• HIV/STI risk reduction counseling<br>• Protocol counseling |
| **Clinical** | | • Collect medical eligibility information (including exclusionary medical conditions and medications)<br>• Collect medical and menstrual history<br>• Collect concomitant medications<br>• Perform physical examination<br>• Perform pelvic examination<br>• Treat or prescribe treatment for RTI/UTI/STIs*<br>• Provide available test results |
| **Laboratory** | **Urine** | • Pregnancy test<br>• Urine dipstick/culture* |
| | **Blood** | • HIV-1 testing<br>• Complete blood count (CBC) with differential and platelets<br>• AST/ALT<br>• Syphilis serology |
| | **Pelvic** | • Nucleic acid amplification test (NAAT) for GC/CT and trichomonas<br>• Pap test^<br>• Saline/potassium hydroxide (KOH) wet mount with pH for candidiasis and/or BV* |
| **Study Product Supply** | | • Offer male condoms |

*If indicated and/or per local standard of care, ^ if indicated (if participant [over age 21] is unable to provide documentation of a satisfactory Pap test within 3 years prior to enrollment)

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

All Enrollment procedures must be performed on the same day. The participant's menstrual cycle must be considered when scheduling Visit 2- Enrollment (Day 0). Ideally,

no bleeding should occur within the first 7 days of product use, e.g., Study Visits 2-6 (Days 0, 1, 2, 3, 7).

**Table 9: Enrollment Visit - Visit 2 (Day 0)**

| Enrollment Visit - Visit 2 (Day 0) | | |
|---|---|---|
| **Component** | | **Procedure/Analysis** |
| **Administrative and Regulatory** | | • Assess and confirm eligibility<br>• Review/update locator information<br>• Randomization<br>• Provide reimbursement<br>• Schedule next visit/contact* |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling<br>• HIV/STI risk reduction counseling<br>• Protocol counseling<br>• Collect product preference/acceptability information<br>• Behavioral assessment |
| **Clinical** | | • Collect medical eligibility information (including exclusionary medical conditions and medications)<br>• Review/update medical and menstrual history<br>• Review/update concomitant medications<br>• Perform targeted physical examination<br>• Perform pelvic examination<br>• Treat or prescribe treatment for RTI/UTI/STIs*<br>• Digital examination by clinician to check VR placement<br>• Provide available test results |
| **Laboratory** | **Urine** | • Pregnancy test<br>• Urine dipstick/culture* |
| | **Blood** | • HIV-1 testing<br>• CBC with differential and platelets*<br>• Plasma for archive<br>• DPV levels▲ |
| | **Pelvic** | • NAAT for GC/CT and trichomonas*<br>• Saline/KOH wet mount with pH for candidiasis and/or BV*<br>• Vaginal swabs for microbiota<br>• Vaginal Gram stain<br>• Cervicovaginal lavage (CVL) for PD and biomarkers ♦<br>• CVF DPV levels▲ |
| | **Rectal** | • Rectal fluid (RF) DPV levels ⌂ |
| **Study Product Supply** | | • Provision of study VR<br>• Insertion of the provided study VR by the participant (or clinician/designee, if necessary)<br>• Provision of study VR use instructions<br>• Offer male condoms |

* If indicated and/or per local standard of care
♦ Collected prior to ring insertion
▲ Samples to be taken 1, 2, and 4 hours following ring insertion
⌂ Sample to be taken 4 hours following ring insertion

## 7.4 Follow-up Visits

### 7.4.1 Day 1, Day 2, Day 3, Day 7, and Day 14 - Visits 3-7

**Table 10: Day 1, Day 2, Day 3, Day 7, and Day 14 - Visits 3-7**

| Day 1, Day 2, Day 3, Day 7, and Day 14- Visits 3-7 | | |
|---|---|---|
| **Component** | | **Procedure/Analysis** |
| **Administrative and Regulatory** | | • Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling*<br>• HIV/STI risk reduction counseling*<br>• Protocol counseling |
| **Clinical** | | • Review/update medical and menstrual history<br>• Review/update concomitant medications<br>• Perform targeted physical examination*<br>• Perform pelvic examination<br>• Treat or prescribe treatment for RTI/UTI/STIs*<br>• Provide available test results<br>• Collect AEs |
| **Laboratory** | **Urine** | • Pregnancy test*<br>• Urine dipstick/culture* |
| | **Blood** | • HIV-1 testing*<br>• CBC with differential and platelets*<br>• Syphilis serology*<br>• DPV levels |
| | **Pelvic** | • NAAT for GC/CT and trichomonas*<br>• Saline/KOH wet mount with pH for candidiasis and/or BV*<br>• CVF DPV levels |
| | **Rectal** | • RF DPV levels Δ |
| **Study Product Supply** | | • Offer male condoms |

* If indicated and/or per local standard of care, Δ Day 3, 7, and 14 (Visits 5, 6, and 7 respectively) only

### 7.4.2 Day 28/Week 4 - Visit 8

**Table 11: Day 28/Week 4 - Visit 8**

| Day 28/Week 4 - Visit 8 | | |
|---|---|---|
| **Component** | | **Procedure/Analysis** |
| **Administrative and Regulatory** | | • Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling*<br>• HIV/STI risk reduction counseling*<br>• Protocol counseling<br>• Collect product use information<br>• Collect product preference/acceptability information<br>• Behavioral assessment |
| **Clinical** | | • Review/update medical and menstrual history<br>• Review/update concomitant medications<br>• Perform targeted physical examination*<br>• Perform pelvic examination<br>• Treat or prescribe treatment for RTI/UTI/STIs*<br>• Provide available test results<br>• Collect AEs |
| **Laboratory** | **Urine** | • Pregnancy test<br>• Urine dipstick/culture* |
| | **Blood** | • HIV-1 testing*<br>• AST/ALT*<br>• CBC with differential and platelets*<br>• Syphilis serology*<br>• DPV levels |
| | **Pelvic** | • NAAT for GC/CT and trichomonas*<br>• Saline/KOH wet mount with pH for candidiasis and/or BV*<br>• Vaginal swabs for microbiota<br>• Vaginal Gram stain<br>• CVF DPV levels<br>• CVL for PK, PD, and biomarkers<br>• Cervical biopsies for PK |
| | **Rectal** | • RF DPV levels |
| **Study Product Supply** | | • Removal and collection of study VR☼<br>• Provision of study VR☼<br>• Insertion of the provided study VR by the participant (or clinician/designee, if necessary) ☼<br>• Provision of study VR use instructions☼*<br>• Offer male condoms |

* If indicated and/or per local standard of care, ☼ For participants randomized to the 25 mg VR

### 7.4.3 Day 56/Week 8 - Visit 9

**Table 12: Day 56/Week 8 - Visit 9**

| Day 56/Week 8 - Visit 9 | | |
|---|---|---|
| **Component** | | **Procedure/Analysis** |
| **Administrative and Regulatory** | | • Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling*<br>• HIV/STI risk reduction counseling*<br>• Protocol counseling<br>• Collect product use information<br>• Behavioral assessment |
| **Clinical** | | • Review/update medical and menstrual history<br>• Review/update concomitant medications<br>• Perform targeted physical examination*<br>• Perform pelvic examination<br>• Treat or prescribe treatment for RTI/UTI/STIs*<br>• Provide available test results<br>• Collect AEs |
| **Laboratory** | **Urine** | • Pregnancy test<br>• Urine dipstick/culture* |
| | **Blood** | • HIV-1 testing*<br>• AST/ALT*<br>• CBC with differential and platelets*<br>• Syphilis serology*<br>• DPV levels |
| | **Pelvic** | • NAAT for GC/CT and trichomonas*<br>• Saline/KOH wet mount with pH for candidiasis and/or BV*<br>• Vaginal swabs for microbiota<br>• Vaginal Gram stain<br>• CVF DPV levels<br>• CVL for PK, PD, and biomarkers |
| **Study Product Supply** | | • Removal and collection of study VR☼<br>• Provision of study VR☼<br>• Insertion of the provided study VR by the participant (or clinician/designee, if necessary)☼<br>• Provision of study VR use instructions☼*<br>• Offer male condoms |

* If indicated and/or per local standard of care, ☼ For participants randomized to the 25 mg VR

### 7.4.4 PUEV/Early Termination Visit Ring Removal - Day 91/Week 13 - Visit 10

**Table 13: PUEV/Early Termination Visit - Visit 10 - Day 91/Week 13**

| PUEV/Early Termination Visit - Visit 10 – Day 91/Week 13 | | |
|---|---|---|
| **Component** | | **Procedure/Analysis** |
| **Administrative and Regulatory** | | • Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling<br>• HIV/STI risk reduction counseling<br>• Protocol counseling<br>• Collect product use information<br>• Collect product preference/acceptability information<br>• Behavioral assessment<br>• In-depth interview (IDI) (Subset)♠ |
| **Clinical** | | • Review/update medical and menstrual history<br>• Review/update concomitant medications<br>• Perform targeted physical examination*<br>• Perform pelvic examination<br>• Treat or prescribe treatment for RTI/UTI/STIs*<br>• Provide available test results<br>• Collect AEs |
| **Laboratory** | **Urine** | • Pregnancy test<br>• Urine dipstick/culture* |
| | **Blood** | • HIV-1 testing<br>• CBC with differential and platelets<br>• AST/ALT<br>• Syphilis serology*<br>• DPV levels∞ |
| | **Pelvic** | • NAAT for GC/CT and trichomonas*<br>• Saline/KOH wet mount with pH for candidiasis and/or BV*<br>• Vaginal swabs for microbiota<br>• Vaginal Gram stain<br>• CVF DPV levels∞<br>• CVL for PK, PD, and biomarkers ►<br>• Cervical biopsies for PK ○ |
| | **Rectal** | • RF DPV levels ○ |
| **Study Product Supply** | | • Removal and collection of study VR<br>• Offer male condoms |

* If indicated and/or per local standard of care
∞ Samples to be taken immediately prior to ring removal, as well as 1, 2, and 4 hours following ring removal
► To be collected after 4-hour CVF sample collection
○ To be collected prior to ring removal
♠ = May be scheduled for different date due to visit length and/or to accommodate participant availability

### 7.4.5 Final Contact - Day 92-94 - Visit 11

This visit should ideally occur between 24 and 72 hours after the PUEV, except for participants who have already had an Early Termination Visit.

**Table 14: Final Contact - Visit 11 - Day 92-94**

| Final Contact - Visit 11 - Day 92-94 | | |
|---|---|---|
| **Component** | | **Procedure/Analysis** |
| **Administrative and Regulatory** | | • Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact* |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling*<br>• HIV/STI risk reduction counseling* |
| **Clinical** | | • Review/update medical and menstrual history<br>• Review/update concomitant medications<br>• Perform targeted physical examination*<br>• Treat or prescribe treatment for RTI/UTI/STIs*<br>• Provide available test results<br>• Collect AEs |
| **Laboratory** | **Urine** | • Pregnancy test*<br>• Urine dipstick/culture* |
| | **Blood** | • CBC with differential and platelets*<br>• DPV levels |
| | **Pelvic** | • Saline/KOH wet mount with pH for candidiasis and/or BV*<br>• CVF DPV levels |
| | **Rectal** | • RF DPV levels |
| **Study Product Supply** | | • Offer male condoms |

* If indicated and/or per local standard of care

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

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

If a participant tests positive for 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, study product use will cease, and the participant will be considered terminated from the study. Participants who become infected after randomization 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-036/IPM 047 SSP Manual for additional details (www.mtnstopshiv.org).

### 7.5.2 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 will be discontinued and the participant will be considered terminated from the study. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained, see Section 9.8 for additional details. Participants who become pregnant while on study product will be offered enrollment in MTN-016 (www.mtnstopshiv.org), (provided their study site is taking part in MTN-016), which includes follow-up throughout the pregnancy and for the first year of the infant's life. For participants who do not enroll in MTN-016, the study site will make every reasonable effort to contact participants and collect infant outcome at approximately one year after delivery for those pregnancies that result in live birth. For additional details regarding obtaining pregnancy outcome, please reference the MTN-036/IPM 047 SSP Manual (www.mtnstopshiv.org).

### 7.5.3 Participants Who Permanently Discontinue Study Product for Other Reasons

For participants who permanently discontinue study product use for any other clinician initiated reason other than HIV seroconversion or pregnancy, site investigators may, after consultation with the PSRT and MTN-036/IPM 047 Management Team, decide to discontinue study follow-up visits and procedures. Participants will, however, be asked to complete all of the procedures scheduled to occur at the PUEV/Early Termination Visit (Visit 10), if willing.

Participants who permanently discontinue study product use due to an AE must continue to be followed in the study, if willing, until resolution (return to baseline) or stabilization of the AE is documented.

In the event study follow-up is continued, participants will have the protocol-specified visits through Final Contact. Protocol-specified procedures will continue except the following:

- Pelvic exams*
- Sample collection for DPV levels
- Sample collection for PK, PD, and biomarkers
- Swabs for microbiota
- Collection of blood for safety assessments*
- Behavioral assessments
- Protocol counseling will be modified

**Unless required for AE follow-up*

The above procedures should be collected/conducted at the visit in which study product is discontinued and omitted thereafter, unless the participant was already on a temporary hold.

*Note: The MTN-036/IPM 047 Management Team, in consultation with the MTN Pharmacology Core, may provide guidance to the site regarding a modified study visit schedule to ensure PK samples are collected at the appropriate time points and/or omitted if the collection of samples would not be anticipated to yield analyzable data. Participants' duration of use and timing of study product permanent discontinuation will be factored into a modified schedule. Refer to the MTN-036/IPM 047 SSP Manual for additional details.*

## 7.6 Interim Visits

Interim visits may be performed at any time during the study, and any visit procedures may be conducted as indicated. All interim contacts and visits will be documented in participants' study records. If a participant misses a visit (e.g., presents to the clinic outside of the visit window), she can return for an interim visit to make up certain missed visit procedures and specimen collections. Refer to the MTN-036/IPM 047 SSP Manual for additional details.

## 7.7 Protocol Counseling: Adherence and Contraception Counseling

Study product and protocol adherence counseling will be provided to all participants upon enrollment into the study. Contraception counseling will be provided to all participants beginning at the Screening Visit. Counseling will be provided in accordance with standard methods, and will include reminders regarding concomitant medications and behavioral restrictions prior to and following collection of biopsies.

## 7.8 Pharmacokinetics

The entire MTN-036/IPM 047 cohort will provide plasma and CVF for PK at Visits 2 through 11. RF will be collected for PK at Visits 2, Visits 5-8, and Visits 10-11.

Detailed instructions are provided in the MTN-036/IPM 047 SSP Manual available at http://www.mtnstopshiv.org.

**Table 15: PK, PD, and Biomarkers Specimen Collection Schedule**

| Visit | Specimens Collected for PK | Specimens Collected for PD *and* to Assess Biomarkers of Mucosal Safety |
|---|---|---|
| Visit 2 – Enrollment (Day 0) | • Blood ▲<br>• Cervicovaginal fluid (CVF) ▲<br>• Rectal fluid ⌂ | • Cervicovaginal lavage (CVL) ♦ |
| Visit 3 - Day 1<br>Visit 4 - Day 2<br>Visit 5 - Day 3<br>Visit 6 - Day 7<br>Visit 7 - Day 14 | • Blood<br>• CVF<br>• Rectal fluid (Visits 5, 6, and 7 only) | |
| Visit 8 - Day 28 | • Blood<br>• CVF<br>• Cervical tissue<br>• CVL<br>• Rectal fluid | • CVL |
| Visit 9 - Day 56 | • Blood<br>• CVF<br>• CVL | • CVL |
| Visit 10 - PUEV/Early Termination Visit (Day 91) | • Blood ∞<br>• CVF ∞<br>• Cervical tissue ○<br>• CVL ►<br>• Rectal fluid ○ | • CVL ► |
| Visit 11 - Final contact (Day 92, 93, or 94) | • Blood<br>• CVF<br>• Rectal fluid | |

♦ Collected prior to ring insertion
▲ To be collected at 1 hour, 2 hours, and 4 hours following ring insertion
⌂ To be collected 4 hours following ring insertion
○ To be collected prior to ring removal
∞ To be collected immediately prior to ring removal, as well as 1 hour, 2 hours, and 4 hours following ring removal
► To be collected after 4-hour CVF sample collection

## 7.9 Behavioral Measures

**Behavioral Assessment**

All participants will complete a Computer-Assisted Self Interview (CASI) baseline questionnaire at the Enrollment Visit. In addition to collecting demographic information, this baseline questionnaire assesses participants' motivation to join the trial, recent sexual behavior, alcohol and drug use, vaginal and sexual practices, partner types, condom use, and other HIV prevention methods used. The assessment includes questions on use of vaginal products, douching practices and other behavioral practices that may affect the vaginal compartment. A subset of these behaviors will be assessed in follow-up

questionnaires, at Visit 8 (Day 28), Visit 9 (Day 56), and Visit 10 (PUEV/Early Termination Visit). Measures used previously in other microbicide trials will be employed.

**Product Adherence Assessment**

Key adherence measures will be captured by CASI and by CRFs to ensure maximum confidentiality of responses. The questions will assess study VR use, report of frequency of study VR removal/expulsions (voluntary and involuntary) and duration without VR inserted in the vagina. A series of questions will ask if the study VR was out, whether it was removed or expelled, under what circumstances or conditions it was removed or expelled, and whether it was re-inserted. A combination of self-administered and interviewer-administered questionnaires will be employed to capture the above information. Study staff will provide participants with guidance on strategies to optimize recall of relevant behavioral and adherence data. This quantitative assessment will be modeled on the adherence assessment for protocols MTN-013, MTN-020 (www.mtnstopshiv.org) MTN-024 and IPM 027 (http://www.ipmglobal.org/). Additionally, at all visits in which a pelvic exam is performed, clinicians will assess whether the VR is in place through visualization on speculum exam and record this assessment on a CRF.

**Product Preference/Acceptability Assessment**

A product preference/acceptability questionnaire will be administered to participants at the Enrollment Visit, Visit 8 (Day 28) and a more thorough questionnaire administered at Visit 10 (PUEV/Early Termination Visit). HIV prevention product preference will also be assessed at the PUEV/Early Termination Visit. This questionnaire includes structured questions about the participant's attitude related to the VR (product characteristics; likes and dislikes concerning the VR), her experiences using the VR (e.g., genitourinary discomfort, ease of use/removal, displacement, willingness to use during menstruation, willingness to use in the future), effect on sex, and partner's reactions. Measures used previously in other microbicide trials will be employed. Specifically, measures related to product preference, which is considered a component of acceptability, will be similar to those used previously in the MTN-001 protocol (for oral vs. vaginal tenofovir), the MTN-024 protocol, and to studies of the VR acceptability and preference as a microbicide delivery method or in contraceptive choice studies.[29, 30]

**In-Depth Interview**

A subset of approximately 24 participants across sites will be randomly selected to complete an in-depth interview (IDI) before exiting from the study. Depending on participant availability and visit length, it may be necessary to conduct this assessment as a separate visit. The IDI will address study VR use and acceptability during the trial. These IDIs will be conducted by a trained qualitative interviewer and will follow a semi-structured questionnaire guide and are anticipated to last approximately 45-60 minutes. Participants will be compensated for the completion of the IDI. These IDIs may be

conducted over the computer. The audio from the IDI will be recorded and transcribed for analysis.

Data on acceptability and factors affecting adherence will be collected during the IDI. The IDIs will include topics such as:

- Challenges to use of study products, specifically in relation to hygiene, menses and sex
- Effect of VR use on sex
- Perceived benefits and barriers to VR use
- Perceived method(s) preferences for HIV prevention and multipurpose prevention technologies

### 7.10 Clinical Evaluations and Procedures

Physical exams will include the following assessments:

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

**may be omitted during targeted physical examinations*

**Pelvic Examination and Specimen Collection**

Pelvic examinations 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.

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.

The required sequence of procedures and specimen collection performed during pelvic exams will be specified in the MTN-036/IPM 047 SSP Manual.

### 7.11 Laboratory Evaluations

Local Laboratory

- Urine
  - Pregnancy test
  - Dipstick/culture

- Blood
  - AST/ALT
  - CBC with differential and platelets
  - HIV-1 testing
  - Syphilis serology

- Pelvic
  - Pap test
  - Saline/KOH wet mount with pH for candidiasis and/or BV
  - NAAT for GC/CT and trichomonas

Network LC

- Blood
  - DPV levels
  - Confirmation HIV-1 testing for seroconversion
  - HIV-1 resistance tests for confirmed seroconverters
  - Plasma for archive

- Pelvic
  - CVF for DPV levels
  - CVL for PK, PD, biomarkers
  - Cervical tissue for PK
  - Vaginal swabs for microbiota
  - Gram stain of vaginal smear

- Rectal
  - RF for DPV levels

Designated Laboratory

- Study Product
  - Used study VR residual drug level assessment (DPV)

Once all required study analyses of collected specimens are complete, any remaining sample may be shipped to the MTN LC for use in study-related quality assurance and

quality control testing. If study samples will be used for assay validation or proficiency testing that is not study related, all participant identifiers will be removed from the samples prior to use. Specimens obtained from participants who do not consent to long term storage will not be used for assay validation or proficiency testing purposes.

### 7.12 Specimen Management

Each study site will adhere to the standards of good clinical laboratory practice (https://www.niaid.nih.gov/sites/default/files/gclp.pdf) in accordance with current US DAIDS Laboratory Requirements, MTN-036/IPM 047 SSP Manual (http://www.mtnstopshiv.org/studies) and site SOPs for proper collection, processing, labeling, transport, and storage of specimens to standardize procedures. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens. 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, and 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.

### 7.13 DAIDS Laboratory Oversight

All laboratories participating in DAIDS Sponsored and/or Funded Laboratories in Clinical Trials will adhere to the DAIDS Laboratory Policy. (https://www.niaid.nih.gov/research/daids-clinical-research-policies-us-labs)

### 7.14 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 U.S. CDC and NIH. All biological specimens will be transported using packaging mandated by US Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous

Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

# 8 ASSESSMENT OF SAFETY

## 8.1 Safety Monitoring

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 sub-group of the Protocol Team, including the Protocol Co-Chairs, DAIDS Medical Officer (MO), Protocol Safety Physician(s), and IPM Safety Physician(s) will serve as the 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 site IoRs 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, 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 staff will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. AE reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS MO and SDMC Clinical Affairs staff, and the IPM safety physician for review.

The PSRT will meet approximately every month, or as needed, 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 or stop the trial may be made by the PSRT at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

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-036/IPM 047. 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 US Food and Drug Administration (FDA) and the Site IoR will notify the responsible IRB expeditiously.

The MTN SMC will also 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 approximately every 4-6 months, or 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 IP and which does not necessarily have a causal relationship with the IP. 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 IP, whether or not considered related to the product. This definition is applied to all study groups beginning at the time of enrollment (i.e., once a participant is randomized) through the termination visit. The term "investigational product" (or IP) for this study refers to all study products.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience. In cases of potentially life-threatening events, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where a study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be captured in the study database. 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 in the study database all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. AEs will be graded per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, March 2017, and Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007]).

In cases where a genital AE is covered in multiple tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

Please note:

- Asymptomatic BV and asymptomatic candidiasis will not be reportable AEs;
- Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs (however, fetal loss data will be collected);
- Untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs;
- Genital bleeding clinically assessed to be expected is not to be reported as an AE.

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

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

### 8.3.3 Adverse Event Relationship to Study Product

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 Adverse Event Reporting Requirements

### 8.4.1 Expedited Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited adverse event (EAE) reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.

For questions about DAERS, please contact NIAID Clinical Research Management System (CRMS) Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.

### 8.4.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study
- The study agents for which expedited reporting is required are the DPV VRs

### 8.4.3 Grading Severity of Events

The grading of severity of events and the reporting period will be the same as for all AEs, as described in Section 8.3.1. The most current DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1, March 2017 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 are available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

### 8.4.4 Expedited AE Reporting Period

The EAE reporting period for this study begins at enrollment and continues through the participant's termination from the study.

After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff becomes 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.

A participant who is pregnant after enrollment will continue to be followed until the pregnancy outcome is ascertained. A participant who becomes pregnant during the course of the study will have study product discontinued and will be terminated from the study; see Section 9.8 for additional details. Pregnancy outcomes will not be expeditiously reported to IPM or the DAIDS 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.

Provided their study site is taking part in MTN-016, a participant who becomes pregnant during the course of study participation will be offered participation in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study. For participants who do not enroll in MTN-016, the study site will make every reasonable effort to contact participants and collect infant outcome at approximately one year after delivery for those pregnancies that result in live birth.

## 8.6 Regulatory Requirements

Information on all reported AEs will be included in reports to the FDA and other applicable government and regulatory authorities. Site IoRs/designees will submit AE and any relevant safety information in accordance with local regulatory requirements.

## 8.7 Social Harms Reporting

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. Social harms that are judged by the IoR/designee to be

serious or unexpected will be reported to the PSRT and responsible site IRBs according to their individual requirements.

# 9 CLINICAL MANAGEMENT

Guidelines for clinical management and temporary product hold/permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to hold study product 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. Unless otherwise specified below, the IoR/designee must immediately consult the PSRT for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs.

Participants reporting any unresolved AEs at the time of study termination will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes, and this information will be documented.

## 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 Temporary Hold and Permanent Discontinuation of Study Product

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

- Acquisition of HIV-1 infection; such participants will not resume product use at any time. The study VR must be held beginning immediately upon recognition of the first reactive rapid HIV test.
- Allergic reaction to the VR
- Pregnancy
- Breastfeeding
- Non-therapeutic injection drug use

A participant will be temporarily discontinued from VR product use by the IoR/designee and a PSRT query submitted for any of the following reasons:

- Reported use of PEP for HIV exposure
- Reported use of PrEP for HIV prevention
- Use of heparin, Lovenox®, warfarin, Plavix® (clopidogrel bisulfate), or other anticoagulant
- Clinical study product hold lasting more than 7 days
- 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. (Temporary hold or permanent discontinuation)

The IoR/designee must consult the PSRT once the temporary hold is initiated. Together, the IoR/designee and the PSRT will discuss resuming product use, continuing the temporary hold, or progressing to permanent discontinuation.

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

**Grade 1 or 2**
In general, a participant who develops a Grade 1 or 2 AE not specifically addressed below, regardless of relationship to study product, may continue product use.

**Grade 3**
Participants who develop a Grade 3 AE not specifically addressed below, judged by the IoR/designee to be not related to study product, may continue product use.

If a participant develops a Grade 3 AE not specifically addressed below and the AE is judged by the IoR/designee to be related to study product, the IoR/designee must temporarily hold study product and consult the PSRT. The hold must continue until a recommendation is obtained from the PSRT.

**Grade 4**
Participants who develop a Grade 4 AE (regardless of relationship to study product), that is not specifically addressed below, must have the study product held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT.

## 9.5 Sexually Transmitted Infection/Reproductive Tract Infection

The IoR/designee must manage STI/RTI per current CDC guidelines, available at http://www.cdc.gov/std/treatment/.

VR use need not be held in the event of an STI/RTI requiring treatment, unless other temporary product hold/permanent discontinuation guidelines described below apply. Should the IoR/designee determine that a temporary product hold is warranted due to an STI or RTI, consultation with the PSRT is required.

## 9.6 Management of Specific Genital Events

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

**Superficial epithelial disruption or localized erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface**

- Continue study VR use (at study clinician's discretion)
- Perform naked eye evaluation
- Re-evaluate by speculum examination in approximately 3-5 days
- If condition worsens or does not resolve at that time, temporarily hold study VR use and consult the PSRT.

**Deep epithelial disruption (ulceration) or generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema or severe edema**

- Temporarily hold study VR
- Perform naked eye evaluation
- Re-evaluate in approximately 3-5 days and resume study VR use if resolved
- If unresolved at reevaluation, continue temporary product hold, and re-evaluate within approximately 2-3 days. If resolved at that time may resume use. If unresolved at this second re-evaluation, continue temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard
- If there is reoccurrence with no identified etiology, continue temporary product hold and consult PSRT regarding permanent discontinuation.

**Unexpected genital bleeding**

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

**Genital petechia(e) and genital ecchymosis**

- Continue study VR use (at study clinician's discretion)
- Perform naked eye evaluation
- No further evaluation or treatment is required.

## 9.7 HIV-1 Infection

Participants who test positive for HIV-1 must have study product permanently discontinued by the IoR/designee. A participant who is confirmed to be HIV-1 positive during the course of the study will have study product discontinued, all follow-up visits will be discontinued and the participant will be considered terminated from the study, as per Section 7.5.1. Guidance regarding management and referral for participants confirmed to be HIV-positive is located in Section 13.10.1.

## 9.8 Pregnancy

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

A participant who becomes pregnant during the course of the study will have study product discontinued and will be terminated from the study, as per Section 7.5.2. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Pregnancy outcomes will be reported on relevant CRFs; outcomes meeting criteria for EAE reporting also will be reported on EAE forms.

A participant who becomes pregnant during the course of study participation may be offered participation in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study, at sites participating in MTN-016. This registry study captures pregnancy outcomes as well as infant health information, (including growth), to evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy.

## 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, NIAID, MTN, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records.

# 10 STATISTICAL CONSIDERATIONS

## 10.1 Overview and Summary of Design

This is a Phase 1, three-arm, multi-site PK and safety study of three silicone elastomer vaginal matrix rings: a VR containing 25 mg DPV and polymer 4870, a VR containing 100 mg DPV and polymer 4870, and a VR containing 200 mg DPV and polymer 4870. A total of approximately 48 healthy, HIV-uninfected women and those assigned female sex at birth will be enrolled and randomized 1:1:1 (16 per arm) to use a study VR. Those randomized to 100 mg or 200 mg VRs will use them continuously for approximately 13 weeks, and they will not be told their group assignment. Participants randomized to 25 mg VRs will replace them every 4 weeks for 8 weeks, then wear them for an additional 5 weeks for a total of 13 weeks.

## 10.2 Study Endpoints

Consistent with the primary study objective to assess the PK of the study VRs used either continuously for 13 weeks (100 mg and 200 mg VRs) or replaced every 4 weeks for 8 weeks and then worn for an additional 5 weeks for a total of 13 weeks (25 mg VR), the following endpoints will be assessed:

- DPV concentrations in plasma
- DPV concentrations in cervicovaginal fluid
- DPV concentrations in cervical tissue

Consistent with the primary study objective to assess safety of the study VRs used either continuously for 13 weeks (100 mg and 200 mg VRs) or replaced every 4 weeks for 8 weeks and then worn for an additional 5 weeks for a total of 13 weeks (25 mg VR), the primary safety endpoints are the proportion of participants with the following:

- Grade 2 or higher genitourinary adverse events as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, March 2017, and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])
- Grade 3 or higher adverse events as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, March 2017

Consistent with the secondary study objective to assess adherence to the study VRs during study participation, the following endpoints will be assessed:

- Frequency of study VR removal/expulsions (voluntary and involuntary) and duration without VR in vagina (by self-report)

- VR use initiation and persistence (whether the VR is in place when participants come to the clinic for their study visits)

Consistent with the secondary study objective to assess acceptability of the study VRs during study participation, the following endpoint will be assessed:

- Degree to which study participants liked or disliked using the three DPV VRs (by self-report)

## 10.3 Primary Study Hypotheses

- Plasma, CVF, and cervical tissue DPV levels will be measurable in all participants
- Continuous exposure to DPV due to sustained release from the 100 mg and 200 mg VR for 13 weeks will be safe
- Dose-proportionality will be demonstrated in tissue and systemic PK

## 10.4 Sample Size and Power Calculations

### 10.4.1 Primary Endpoints

The proposed total sample size is approximately N=48 randomized into 3 arms in a 1:1:1 ratio giving 16 participants per group.

PK endpoints will include the DPV concentration assessed in plasma, CVF, and cervical tissue. DPV concentrations on day 28, 56 and 91 will be described and compared between the 100 mg VR, the 200 mg VR, and the 25 mg VR arms.

Approximately 16 participants in each arm will provide plasma, CVF and cervical tissues. The CV% of the DPV concentrations ranges from 45% to 61% depending on time and location for the 25 mg VR (IPM 015). If one assumes a CV% of 50%, and a similar standard deviation across the three arms, then with 5% type I error and 80% power, we can exclude a difference as large as 1.02 SD units or a 51% difference.

As a means to characterize the statistical properties of this study, Table 16 presents the probability of observing zero, at least one and two or more safety endpoints among the 16 participants in each group given a true event rate.

**Table 16: The probability of observing a number of participants of having a safety event given the true event rate and the sample size in the group**

| 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 |
| 20% | 0.028 | 0.972 | 0.859 |
| 25% | 0.010 | 0.990 | 0.937 |

This is a Phase 1 study and therefore not powered to detect small differences in rates of safety endpoints between two arms. Table 17 provides the difference in the rates of safety events between the extended duration DPV VR (100 mg or 200 mg) arm and the 25 mg DPV VR arm that is detectable for a given rate in the 25 mg DPV arm, assuming a two-sided Fisher's exact test with $\alpha$=0.05 and 80% or 90% power. For example, if the true rate of a given toxicity endpoint in the 25 mg DPV arm is 6.25% (1 out of 16 participants experiencing a safety event), the sample size N=48 provides 80% power to detect safety endpoint rates greater than 56.3% in the extended duration DPV VR (100mg or 200 mg) arm (62.5% with 90% power).

**Table 17: Difference in the Observed Rates of Safety Events***

| True rate in 25 mg DPV arm, percentage (fraction) | Observed rate in extended duration DPV VR (100mg or 200mg) arm detectable with 80% power, percentage (fraction) | Observed rate in extended duration DPV VR (100mg or 200mg) arm detectable with 90% power, percentage (fraction) |
|---|---|---|
| 6.25 (1/16) | 56.3 (9/16) | 62.5 (10/16) |
| 12.5 (2/16) | 68.8 (11/16) | 75.0 (12/16) |
| 18.8 (3/16) | 75.0 (12/16) | 81.3 (13/16) |
| 25.0 (4/16) | 81.3 (13/16) | 87.5 (14/16) |
| 31.3 (5/16) | 87.5 (14/16) | 93.8 (15/16) |

* Note: the figures in this table represent examples and are not actual rates of adverse events.

### 10.4.2 Secondary Endpoints

#### Adherence Endpoint

Adherence will be measured by the percentage of participants who keep the VR inserted at all times in the vagina over the study period. A sample size of 48 participants will provide an absolute precision of 12.9% (i.e., half the width of the 95% confidence interval) assuming an observed adherence of 75%.

#### Acceptability Endpoint

The acceptability of the study VR will be determined by participants rating several components of attitudes about VR attributes (e.g., dosing regimen, and willingness to use this VR in future) on a combination of categorical and continuous scales. A sample size of 32 participants receiving the 100mg or 200mg DPV VR will provide an absolute

precision of 15.8% (i.e., half the width of the 95% confidence interval) assuming an observed acceptability of 75%.

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

Based on previous studies of vaginal products with similar eligibility requirements, the accrual of 48 eligible participants will take approximately 6-9 months. Participants lost to follow-up and/or on temporary hold or permanent product discontinuation will not be replaced. However, every effort will be made to complete their regularly scheduled safety evaluations. Additionally, participants who are found to be HIV-infected and/or pregnant after enrollment will be terminated from the study and will not be replaced. Each site will target retention of 95% of enrolled participants over the 13-week follow-up period.

## 10.6 Randomization

The participants will be randomized using permuted block randomization in a 1:1:1 ratio to the three arms of the study. Study arm randomization will be stratified by site to ensure balanced assignment for products at each site. In addition, approximately 24 participants will be randomly selected for IDIs.

The randomization scheme will be generated and maintained by the MTN SDMC.

## 10.7 Data and Safety Monitoring and Analysis

### 10.7.1 Study Monitoring Committee

Data and Safety Monitoring Board oversight is not planned for this study. The MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, study or lab issues, and a closed safety data report to voting SMC members. The review will take place at least once during the study, and as needed.. At the time of this review, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. For further information regarding the SMC, please reference the MTN Manual of Operational Procedures (www.mtnstopshiv.org).

### 10.7.2 Primary Analysis

All participants randomized into the study will be included in the primary analysis according to principle of Intent-to-Treat.

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Within-treatment group assessment of the change from the baseline measurement to a follow-up measurement will be analyzed

using McNemar's test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). When use of formal testing to assess differences between users of the 100 mg or 200 mg VR and users of the 25 mg VR is required, the following methods will be used: for binomial response variables, chi-square tests and logistic regression (or exact testing methods); for continuous variables, t-tests and linear regression or nonparametric methods if data are non-Normal.

To assess the adequacy of the randomization, participants in each arm will be compared for baseline characteristics including demographics and laboratory measurements using descriptive statistics. Due to the small sample size, formal comparisons will not be done.

**Pharmacokinetic Analysis**

The DPV concentrations based on the samples obtained as described above will be summarized using descriptive statistics for each study arm on day 28, 56 and 91. The mean DPV concentration from the 100 mg (200 mg) VR arm will be compared to the mean from the 25 mg VR arm at each sample collection time (day 28, 56, and 91) for each matrix – plasma, CVF, and cervical tissues.

**Safety Analysis**

To assess safety, the number and the percentages of participants experiencing each safety endpoint will be tabulated by study arm. 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 for each arm and Fisher's exact test used to test for differences in event rates between the extended duration VR (100 mg or 200 mg) arm and the 25 mg VR arm.

### 10.7.3 Secondary Analyses

**Adherence Analysis**

To assess adherence of participants to the assigned VR, the proportion of participants who kept the study VR inserted at all times during the 91 days will be calculated along with a 95% confidence interval. For participants who were not fully adherent, the number of removal/expulsion events and average duration of these events will be reported. Number, type and circumstances of expulsions (voluntary and involuntary) will be described.

**Acceptability Analysis**

To assess acceptability of the study products, summary statistics will be calculated on each component of acceptability by arm (extended duration VR and 25 mg VR arms). The number and percentage of participants who find the study VRs to be at least as

acceptable as other HIV prevention methods will also be calculated by arm.

### 10.7.4 Missing Data

In any situation with missing data, appropriate secondary analyses will be performed to adjust for variables that may be related to the missingness mechanism. If missing data rates are higher than 10%, covariates that are related to missingness in likelihood-based regression models will be included. A sensitivity analyses to assess the potential impact of the missing data will also be performed. These analyses will include imputing the data under the most extreme scenarios of information missingness, such as assuming everyone missing has an extreme value of the missing variable, and less informative imputation approaches.

# 11 DATA HANDLING AND RECORDKEEPING

## 11.1 Data Management Responsibilities

Data collection tools will be developed by the MTN SDMC in conjunction with the protocol team. Quality control and data integrity are managed manually and systematically with reports and queries routinely generated and provided by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site will identify all CRFs to be used as source documents, and will submit test CASI data to confirm proper data transfer to the SDMC. Study CRF data will be entered and cleaned using the Medidata Rave electronic data capture (EDC) tool, a data management system compliant with the ICH Good Clinical Practices (GCP) and US CFR guidelines for EDC.

Transcriptions of interviews will be generated in the field and electronically transferred to RTI using a secure File Transfer Protocol site, where they will be uploaded and managed using a qualitative software package. RTI will act as a hub, and manage all qualitative data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. RTI will save all versions of all files on a secure, password-protected server.

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

All study sites will maintain source data/documents in accordance with current DAIDS policies. (https://www.niaid.nih.gov/sites/default/files/documents/daids-sourcedocpolicy.pdf)

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 IPs, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval for the study product being tested for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US FDA is notified.

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

### 11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with current DAIDS policies.
(https://www.niaid.nih.gov/sites/default/files/documents/qmppolicy.pdf)

## 12 CLINICAL SITE MONITORING

Study monitoring will be carried out by Pharmaceutical Product Development, Inc. (PPD) (Wilmington, NC) in accordance with current DAIDS policies. On-site study monitoring will be performed in accordance with current DAIDS policies. Study monitors will visit the site to do the following:

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

The IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., ICFs, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the MTN Coordinating LOC, SDMC, LC, IPM, NIAID, FDA, OHRP, IRBs 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 every effort 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, SDMC, and other local and US regulatory authorities or any of their appointed agents.

## 13.1 Institutional Review Boards/Ethics Committees

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

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

## 13.2 Protocol Registration

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

protocol registration packet to ensure that all of the required documents have been received.

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

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

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

### 13.3 Study Coordination

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

Study implementation will be directed by this protocol, which may not be amended without proper regulatory approvals. Study implementation will also be guided by a common SSP manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN 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

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

Vaginal Fluid Collection
Collection of vaginal fluid may cause discomfort or pressure in the vagina or genital area.

Rectal Fluid Collection
Insertion of a lubricated anoscope to collect rectal fluid will likely cause some discomfort or pressure in the rectum or anorectal area. There is the risk of mild discomfort in addition to a slight risk of bleeding with the insertion of rectal swabs or sponges.

Pelvic Examination and Procedures
Pelvic examination and procedures may cause mild discomfort, pressure and/or vaginal bleeding or spotting.

Cervical Biopsy Collection
Cervical biopsies carry the risk of discomfort or pain during the procedure and for a few hours afterwards. Participants may have mild vaginal spotting (bleeding) for one or two days. Participants will be instructed not to use aspirin (over 81 mg per day) and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours before and after the collection of the cervical biopsies. Participants are to abstain from sexual activities for 72 hours following cervical biopsy collection. If participants engage in sexual intercourse before the biopsy has healed they may experience some temporary discomfort. If participants are sexually active they may also be at increased risk for STIs and HIV acquisition, if exposed. There is a small risk of infection and heavier bleeding. Participants will be instructed to contact the clinic if symptoms are bothersome, if heavy bleeding is noted (soaking through a pad in an hour or less) or if the participant develops any abnormal odor or discharge from the vagina.

Phlebotomy
Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling, having a blood clot and/or infection.

Other Risks
Being tested for HIV and STIs and waiting for your test results may cause worry, sadness or depression. Provision of positive test results 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 and alcohol and drug use.

Participants at sites where local regulatory authorities require partner notification in response to diagnosed STI or HIV infection could have problems in participants' relationships. Participants also could have problems in their partner relationships associated with use of study product and abstinence requirements.

Participants may be asked questions about their study product use, vaginal and sexual practices, menstrual hygiene, and alcohol and drug use. These questions may make some participants uncomfortable.

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 others may think participants are 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, communities, and/or employer(s).

Risks Associated With Study Vaginal Ring

Use of the study VR may lead to vaginal symptoms, including irritation, increased discharge, and discomfort (including with vaginal intercourse if it were to occur). 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 two previous Phase 3 studies with the DPV VR (ASPIRE [MTN-020] and The Ring Study [IPM 027]), frequently reported AEs (occurring in ≥ 10% of trial participants)[6, 13, 14] are listed below:

- Vaginal discharge
- Itching of the vagina
- Female genital infection
- Vaginal yeast infection
- Bacterial vaginosis (vaginal infection)
- STIs (Chlamydia, gonorrhea, trichomonas)
- Pelvic pain
- Abnormal uterine bleeding, including prolonged, heavy, or excessive bleeding and irregular or more frequent bleeding
- Urinary tract infection
- Upper respiratory tract infection
- Abnormal weight loss
- Decreased blood counts (red or white blood cells)
- Increased liver enzymes in the blood

It should be noted that a causal association between the above side effects and the study products has not yet been determined. There were no significant differences between the

DPV VR and placebo groups in frequency of safety endpoints.

Toxic shock syndrome has been reported with currently marketed contraceptive VRs, though a causal relationship between the two has not been established.[31] As with any vaginally retained product, the possibility of toxic shock syndrome, although rare, exists. Detailed information regarding the plan for diagnosis and management of this condition should it arise is provided in the MTN-036/IPM 047 SSP Manual.

Based on in vitro data, HIV-infected participants who have prolonged exposure to low concentrations of DPV 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.

### 13.4.2 Benefits

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

Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of safe and effective interventions to prevent HIV transmission. Information learned in this study may also help to understand issues important for broader implementation of the DPV ring. Participants may also appreciate the opportunity to contribute to the field of HIV prevention research.

## 13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to screening. Written informed consent also will 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 (https://www.niaid.nih.gov/sites/default/files/documents/daids-sourcedocpolicy.pdf). Participants will be provided with copies of the ICFs if they are willing to receive them.

In addition to ICFs, 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 SSP manual.

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

- The unknown safety and unproven efficacy of the 100 mg and 200 mg DPV VRs
- Randomization and the importance of participants in all of the study groups to the success of the study
- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The real yet limited benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

### 13.6 Participant Confidentiality

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

All study-related information will be stored securely. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers to identifying information will be stored in a separate, locked file in an area with limited access. After receiving appropriate approval, all study documents/data will be properly disposed of, including the proper destruction and/or deletion of paper files, electronic study data, and electronic documents. 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, OHRP, NIH, and/or contractors of the NIH

- Representatives of IPM
- Representatives of the MTN LOC, SDMC, and/or LC
- Study staff
- Site IRBs

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

## 13.7 Special Populations

### 13.7.1 Pregnant Women

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

### 13.7.2 Children

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

## 13.8 Compensation

Pending IRB approval, participants will be compensated for time and effort in this study, and/or be reimbursed for travel to study visits. Site specific compensation amounts will be specified in the study ICFs of each individual site.

## 13.9 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV-1 identified among study participants to health authorities. Participants will be made aware of reporting requirements during the informed consent process.

### 13.10 Access to HIV-related Care

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

#### 13.10.1 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 the Enrollment Visit, follow-up procedures will be performed as per Section 7.5.1. Please refer to Section 9.7 for further details.

### 13.11 Study Discontinuation

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

## 14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies and a CTA between NIAID and IPM will govern publication of the results of this study.

# 15 APPENDICES

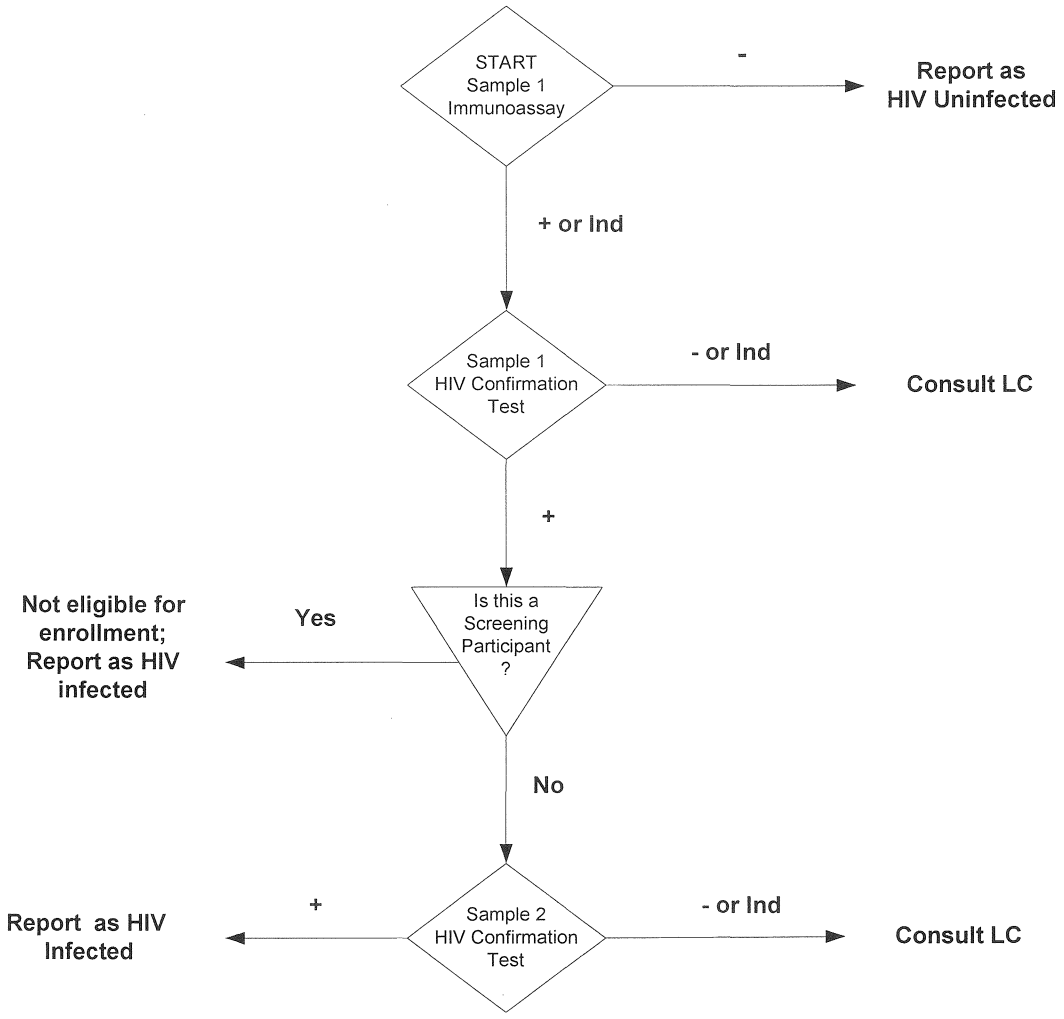
# APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

| | Visit 1 SCR | Visit 2 ENR (Day 0) | Visits 3-7 (Days 1, 2, 3, 7, and 14) | Visit 8 (Day 28/ Week 4) | Visit 9 (Day 56/ Week 8) | Visit 10 PUEV/Early Termination (Day 91/ Week 13) | Visit 11 Final Contact (Day 92, 93 or 94) |
|---|---|---|---|---|---|---|---|
| **ADMINISTRATIVE AND REGULATORY** | | | | | | | |
| Obtain written informed consent(s) | X | | | | | | |
| Assign a unique Participant Identification (PTID) number | X | | | | | | |
| Assess and/or confirm eligibility | X | X | | | | | |
| Collect demographic and background information | X | | | | | | |
| Collect/review/update locator information | X | X | X | X | X | X | X |
| Randomization | | X | | | | | |
| Provide reimbursement | X | X | X | X | X | X | X |
| Schedule next visit/contact | * | * | X | X | X | X | * |
| **BEHAVIORAL/COUNSELING** | | | | | | | |
| HIV pre- and post-test counseling | X | X | * | * | * | X | * |
| HIV/STI risk reduction counseling | X | X | * | * | * | X | * |
| Protocol counseling | X | X | X | X | X | X | |
| Collect product use information | | | | X | X | X | |
| Collect product preference/ acceptability information | | X | | X | | X | |
| Behavioral assessment | | X | | X | X | X | |
| In-depth interview (IDI) | | | | | | X♠ (subset) | |
| **CLINICAL** | | | | | | | |
| Collect medical eligibility information (including exclusionary conditions and medications) | X | X | | | | | |
| Collect/review/update medical/menstrual history | X | X | X | X | X | X | X |
| Collect/review/update concomitant medications | X | X | X | X | X | X | X |
| Perform physical exam (Targeted at Visits 2-11) | X | X | * | * | * | * | * |
| Perform pelvic exam | X | X | X | X | X | X | |
| Treat or prescribe treatment for RTI/UTI/STIs | * | * | * | * | * | * | * |
| Digital exam by clinician to check VR placement | | X | | | | | |
| Provide available test results | X | X | X | X | X | X | X |
| Collect AEs | | | X | X | X | X | X |
| **LABORATORY** | | | | | | | |
| URINE | Pregnancy test | X | X | * | X | X | X | * |
| | Urine dipstick/culture | * | * | * | * | * | * | * |

| | | Visit 1 SCR | Visit 2 ENR (Day 0) | Visits 3-7 (Days 1, 2, 3, 7, and 14) | Visit 8 (Day 28/ Week 4) | Visit 9 (Day 56/ Week 8) | Visit 10 PUEV/Early Termination (Day 91/ Week 13) | Visit 11 Final Contact (Day 92, 93 or 94) |
|---|---|---|---|---|---|---|---|---|
| BLOOD | HIV-1 testing | X | X | * | * | * | X | |
| | Plasma for archive | | X | | | | | |
| | AST/ALT | X | | | * | * | X | |
| | CBC with differential and platelets | X | * | * | * | * | X | * |
| | Syphilis serology | X | | * | * | * | * | |
| | DPV levels | | ▲ | X | X | X | ∞ | X |
| PELVIC | NAAT for GC/CT and trichomonas | X | * | * | * | * | * | |
| | Saline/potassium hydroxide (KOH) wet mount with pH for candidiasis and/or bacterial vaginosis (BV) | * | * | * | * | * | * | * |
| | Pap test | X^ | | | | | | |
| | Vaginal swabs for microbiota | | X | | X | X | X | |
| | Vaginal Gram stain | | X | | X | X | X | |
| | CVF DPV levels | | ▲ | X | X | X | ∞ | X |
| | CVL for PK, PD, and biomarkers | | ♦ | | X | X | X► | |
| | Cervical biopsies for PK | | | | X | | X○ | |
| RECTAL | RF DPV levels | | X ⌂ | X Δ | X | | X○ | X |
| **STUDY PRODUCT SUPPLY** | | | | | | | | |
| Provision of study VR | | | X | | ☼ | ☼ | | |
| Insertion of the provided study VR by the participant (or clinician/designee, if necessary) | | | X | | ☼ | ☼ | | |
| Provision of study VR use instructions | | | X | | ☼* | ☼* | | |
| Removal and collection of study VR | | | | | ☼ | ☼ | X | |
| Offer male condoms | | X | X | X | X | X | X | X |

X Required
* If indicated and/or per local standard of care
^ If participant [over age 21] is unable to provide documentation of a satisfactory Pap test within 3 years prior to enrollment
▲ Samples to be taken 1, 2, and 4 hours following ring insertion
♦ Collected prior to ring insertion
► To be collected after 4-hour CVF sample collection
⌂ Sample to be taken 4 hours following ring insertion
○ To be collected prior to ring removal
∞ Samples to be taken immediately prior to ring removal, as well as 1, 2, and 4 hours following ring removal
Δ Visits 5, 6, and 7 only (Days 3, 7 and 14 respectively)
☼ For participants randomized to the 25 mg VR
♠ May be scheduled for later date due to visit length and/or to accommodate participant availability

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




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-036/IPM 047**
**Version 1.0**
**June 28, 2017**

### A Phase 1, Randomized Pharmacokinetics and Safety Study of Extended Duration Dapivirine Vaginal Rings

**PRINCIPAL INVESTIGATOR:** [Sites to insert]
**PHONE:** [Sites to insert]
**SHORT TITLE:** PK and Safety Study of Extended Duration DPV VRs

### INFORMED CONSENT

You are being asked to take part in this research study because you:

- were assigned female sex at birth
- are HIV-negative
- are healthy
- are between the ages of 18 and 45 years old

Approximately 48 people who agree to use contraception for the duration of their study participation will take part in this study at two sites in the United States. This study is sponsored by the US National Institutes of Health (NIH) and conducted by the Microbicide Trials Network (MTN). The study products in this clinical trial include three vaginal rings (VR) containing the anti-HIV medication, dapivirine (DPV), in three different doses. If you agree to take part in this study, you will wear a VR for 13 weeks. The VR is made out of flexible plastic. You will be asked to attend clinic visits while wearing the ring and one day in the three days after the ring is removed. The study rings are supplied by the International Partnership for Microbicides (IPM), a not-for-profit research organization. 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 have read this form 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 form 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).

## WHAT IS THE PURPOSE OF THIS STUDY?

The main purpose of this research study is to find out how the study drug, dapivirine (DPV), enters and exits the body when a ring containing a dose of either 100mg DPV or 200mg DPV is inserted into the vagina and left in place for 13 weeks (approximately 91 days), as compared to a 25 mg DPV VR used for 4 or 5 weeks at a time. Another purpose of this study is to find out if these two doses are safe and well tolerated for use over a longer period. This study will provide important information about the higher dose, extended use DPV VRs when used by people of childbearing age.

## STUDY PRODUCT

HIV is the virus that causes AIDS. DPV works by preventing HIV from making copies of itself, which stops the spread of HIV in the body. DPV VRs containing 25 mg DPV have been previously tested and found to be generally safe and well-tolerated. Also, two large studies recently showed the 25 mg DPV VR can lower the chances of becoming infected with HIV when used as directed. Study staff can provide you with additional information about these studies if you are interested in learning more.

While the study drug has been tested before in humans, this is the first time that these VRs containing 100 mg or 200 mg DPV have been studied in humans. Based on available data, these higher-dose, extended use VRs are not expected to deliver more DPV throughout the body than has been shown to be safe and well-tolerated in earlier studies in which DPV was taken orally. Study staff will closely monitor all participants over the period of planned study product use to respond quickly to any safety concerns.

## STUDY GROUPS

Approximately 48 eligible participants will be equally assigned by random chance (like a roll of the dice) to one of three VR study groups:

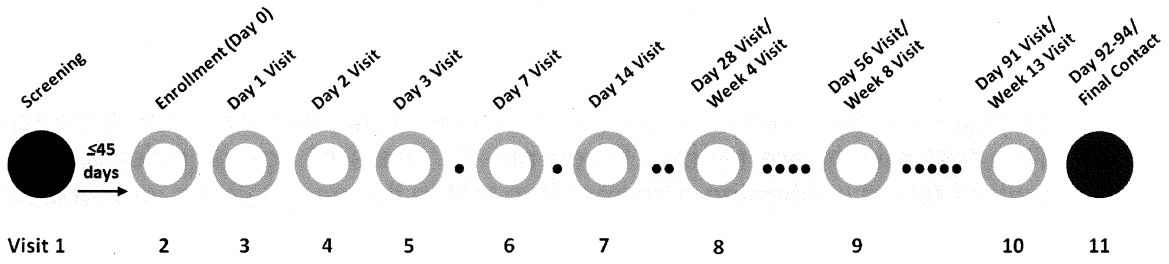
- A ring containing 25 mg DPV, to be replaced twice during 13 weeks of use
- A ring containing 100 mg DPV, to be worn continuously for 13 weeks
- A ring containing 200 mg DPV, to be worn continuously for 13 weeks

Approximately 16 participants will be assigned to each of the three study groups. This means that approximately two thirds of participants will use a single VR (100 or 200 mg DPV) continuously for 13 weeks. The other third will also use a VR (25 mg DPV) for 13 weeks, but will replace it twice during that time, after the 4$^{th}$ and 8$^{th}$ week of use. Participants will be assigned to a group by random chance, and neither you nor the study staff can control which group you will be assigned to. If you are assigned to use a single

VR continuously for 13 weeks, you will not be told if you were assigned to the 100 or to the 200 mg DPV VR. You will be told if you are assigned to the 25 mg DPV VR.

## WHAT WILL HAPPEN DURING THE STUDY VISITS?

The study includes a total of eleven (11) clinic visits, including the Screening Visit today. All visits will take place at this clinic.




### Screening Visit Procedures:

The procedures done today will take about ***[SITES TO INSERT TIME]***. Study staff will:

- Ask you questions to confirm that you are able to join the study.
- Ask you to provide them with your contact information (i.e., where you live and how we can get in touch with you).
- Ask you questions about your medical health (including what medications you are taking), menstrual history, sexual behaviors, drug and alcohol use, and your understanding of the study requirements. They may also ask to view your medical records with your permission.
- 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.
- 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.
  - You will answer questions about whether and for how long you have been using an effective method of contraception, and whether you intend to use this method for the entire time that you are in this study. Effective methods include:
    - Sterilization by you or your partner (tubal ligation, vasectomy, etc.).
    - Hormonal methods except contraceptive rings.
    - Intrauterine devices (IUDs) inserted at least 30 days before enrollment.
    - Having sex exclusively with others having female genitalia exclusively.
    - Abstinence from penile-vaginal intercourse for 90 days before enrollment and planning to remain abstinent for the duration of study participation.

- Perform a physical examination.
- Perform a pelvic examination:
  - The study clinician will use a speculum (a plastic or metal instrument inserted in the vagina). Study staff will ask if you are experiencing symptoms of an infection. They will check your vagina and cervix for signs of infection and other problems.
  - A small amount of vaginal fluid will be collected via swab(s), like a Q-tip. 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 older than 21, the study staff may also collect samples from your cervix for a "Pap test" or "Pap smear". Study staff will inform you of the results of your Pap test. It takes about [SITES TO INSERT AMOUNT OF TIME] before Pap test results are ready. If you are 21 years of age or older and have a written report confirming a normal Pap test in the past 3 years, or if you had an abnormal Pap test but had follow-up indicating no treatment was required, you will not need to have a Pap test taken at this screening visit. The results of your Pap test may affect whether or not you can join the study.
- Take a blood sample [SITES TO INSERT AMOUNT]:
  - To test the health of your blood and liver.
  - To test for infections typically 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 STIs. 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 STIs or other urinary or reproductive tract infections.
- 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].
- Give you male condoms, if you need them.
- Reimburse you for your visit.
- Schedule your next visit to enroll in the study, if you are willing and eligible.
  - Your menstrual cycle will be considered when scheduling your next visit because, ideally, no bleeding should occur on the first 7 days of product use.

It may be necessary to conduct more than one clinic visit to complete all required screening procedures.

If you do not join the study, blood and other samples collected at the Screening visit(s) will not be kept or used for any tests other than those listed above.

If you enroll in the study, you will be asked to abstain from sexual practices, tampon use and other non-study products for specified periods of time prior to your clinic visits. See stated length of time highlighted below:

| *Activity:* | *For How Long?* |
|---|---|
| Receptive sexual practices, including:<br>• Penile-vaginal intercourse<br>• Penile-anal intercourse<br>• Receptive oral intercourse<br>• Finger stimulation | For 72 hours before each clinic visit |
| Tampon use | For 24 hours before each clinic visit |
| Inserting any objects into your vagina or rectum, including:<br>• Sex toys<br>• Female condoms<br>• Diaphragms<br>• Menstrual cups<br>• Cervical caps or any other vaginal barrier method | For the duration of study participation beginning 24 hours before the enrollment visit |
| Using any vaginal or anal products, including:<br>• Spermicides<br>• Lubricants<br>• Contraceptive VRs<br>• Douches<br>• Vaginal medications<br>• Vaginal moisturizers | For the duration of study participation beginning 24 hours before the enrollment visit |

**Enrollment and Follow-up Visit Procedures:**

If you are found to be eligible, your next visit will be within 45 days of your Screening Visit today, and is called the Enrollment Visit. The procedures done during the Enrollment Visit will take about ***[SITES TO INSERT TIME]***. This visit will take longer than most because we will check your blood and vaginal fluids over a period of 4 hours after the ring is inserted.

At your Enrollment Visit, study staff will:

- Ask you questions to confirm you are able to join the study.
- Randomly assign you to one of three study groups. Participants in all study groups will have the same study visit schedule.
- Give you the study VR to insert at the clinic. Study staff may help you insert the VR if you cannot do it on your own. All participants will have an examination to ensure the ring is inserted correctly.
  - You will be asked to keep the VR in place and not remove it between visits. Participants assigned to the 25 mg DPV VR study group will be asked to remove their study VR at the 4-week and 8-week study visits (Visits 8 and 9) and replace it with a new ring.
  - Study staff will show you how to take the ring out in case you need to.

    - Study staff will talk with you about what to do if you have any problems or symptoms while using the ring.
- Take blood samples ***[SITES TO INSERT AMOUNT]*** at several time points, before the study VR is inserted and at one, two, and four hours after it is inserted. An intravenous cannula (IV tube) may be placed, flushed with sterile salt water, and kept in place for up to 4 hours after you insert the study VR for the blood draws; it will be removed before you leave the clinic.
    - The blood samples will be collected:
        - For HIV testing.
        - For research purposes, to measure the amount of DPV in your body over time.
        - In case there is a question about your lab results in the future.
        - The same tests may be done when these samples are collected at future visits.
- Collect a small amount of vaginal fluid via swab at several time points, before the study VR is inserted and at one, two, and four hours after it is inserted. A clinician will insert the swab approximately 3 inches inside your vagina.
    - Swabs will be collected:
        - For STI testing, if needed.
        - For research purposes, to measure the amount of DPV and bacteria present in the vagina when using the study VR.
        - The same tests may be done when these samples are collected at future visits.

At most study visits, including the Enrollment Visit, study staff will:

- Ask you to update your contact information.
- Talk with you about the requirements of the study and how to follow them, including keeping the VR in place and not removing it between visits as well as restrictions on vaginal and sexual practices.
- Talk with you about STIs, HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex.
- Ask you about your sexual behaviors and drug and alcohol use, and about any health or medical problems you may be currently experiencing or that have occurred since your last visit (including what medications you are taking).
- Ask you about any menstrual periods or spotting you may have had since your last visit.
- Ask you questions about vaginal practices that may affect how your body absorbs the study drugs.
- Ask you questions about your study product use and about your thoughts on the study product.
    - You may use a computer to answer these questions. It is important that you know that you will answer these questions in private and your responses will be kept confidential.

- Talk with you about any problems or symptoms that you encounter as a result of wearing the VR or undergoing any of the study procedures.
- Test your urine for pregnancy and, if needed, for infections.
- Take blood samples ***[SITES TO INSERT AMOUNT]*** to test your health and for research purposes.
- Give you a physical examination.
- Give you a pelvic examination.
  - The study clinician will use a speculum to check your vagina and cervix for signs of problems due to the ring or infection. They may also collect vaginal fluid to test for infections and for research purposes.
  - At the Enrollment, 4-week, 8-week, and 13-week clinic visits (Visits 2, 8, 9, and 10), a cervicovaginal lavage (CVL) will be performed. For the CVL, a clinician rinses your vagina and cervix with a small amount of sterile fluid and collects that fluid in a tube for testing. The CVL fluid collected will be used for research purposes only.
  - At the 4-week and 13-week clinic visits (Visits 8 and 10), a cervical biopsy will be performed. Study clinicians will take approximately 2 small tissue samples from your cervix, each about the size of a grain of rice. These samples will be used to see how much of the study drug is in your tissue. It is important that you do not put anything in your vagina for 3 days before the collection of the biopsies and 3 days after, to include avoiding sexual intercourse, because you may be at higher risk for getting or spreading an infection until the biopsy sites have healed. It is also important that you do not take any aspirin doses higher than 81 mg per day for 3 days before and after the collection of the cervical biopsies, because you may be at higher risk of bleeding.
- Take rectal fluid samples. At the Day 0, Day 3, Day 7, Day 14, Day 28, , Day 91, and Day 92-94 clinic visits (Visits 2, 5, 6, 7 and 8, 10, and 11), the study clinician will use an anoscope (a short hollow tube inserted in your rectum) to collect rectal fluid for research purposes.
- Give you treatment or refer you for treatment for any issues they may find.
- Give you your test results, if available.
- Give you condoms, if you need them.
- Be reimbursed for your visit.
- Schedule your next visit, if applicable.

As with the Enrollment visit, your 13-week study visit (Visit 10, when the study VR is removed) will take longer than most because we will check your blood and vaginal fluids over a period of 4 hours after the ring is removed. During this visit, study staff will:

- Take blood samples ***[SITES TO INSERT AMOUNT]*** at several time points, before removal of the study VR and at one, two, and four hours after it is removed. An intravenous cannula (IV tube) may be placed, flushed with sterile salt water, and kept in place for up to 4 hours after you remove the study VR for the blood draws; it will be removed before you leave the clinic.

- Collect a small amount of vaginal fluid via swab at several time points, before removal of the study VR and at one, two, and four hours after it is removed.
- Collect the study VR from all participants.

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

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

**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 one or more of the following:

- Issues with sample processing, testing or shipping.
- If you are experiencing any symptoms or changes in your physical condition.
- If tests or procedures were missed or not conducted.

Additional testing may be performed as part of quality control.

**In-depth Interview Subset:**
You may be asked to participate in an interview with a trained staff member to discuss your experiences during study participation. If you are asked to participate in this interview, you will be asked questions about your use of the ring, your preferences and opinions, your experiences with using the ring during sex, any problems you may have had using the ring, and whether you used the VR or not. The interviews will be audio-recorded to make sure to record your words exactly how you said them. The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or made up names, and the hardware will be physically protected in a locked area. This means that no one other than the MTN-036 study team will have access to your responses. The information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-036 study team for the purposes of this research.

## RISKS AND/OR DISCOMFORTS

**Risks of Blood Draws**
Whenever your blood is drawn, you may have:

- Discomfort.
- Feelings of dizziness or faintness.
- Bruising, swelling, small clot and/or infection.

**Risks of Pelvic 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.

Cervical biopsies carry the risk of discomfort or pain during the procedure and for a few hours afterwards. You may have spotting (bleeding) for one or two days. With cervical biopsies there is also a small risk of infection and heavier bleeding. You may also be at increased risk for STIs and HIV acquisition, if exposed. You will be encouraged to call the clinic to report any problems after the collection, especially if heavy bleeding is noted (soaking through a pad or tampon in an hour or less) or if you develop any abnormal vaginal odor or discharge.

**Risks of Dapivirine Vaginal Rings**

DPV VRs may be associated with the side effects listed below based on side effects reported among participants in previous studies of DPV VRs and VRs without study drug:

- Vaginal discharge
- Itching of the vagina
- Female genital infection
- Vaginal yeast infection
- Bacterial vaginosis (vaginal infection)
- STIs (Chlamydia, gonorrhea, trichomonas)
- Pelvic pain
- Abnormal uterine bleeding, including prolonged, heavy, or excessive bleeding and irregular or more frequent bleeding
- Urinary tract infection
- Upper respiratory tract infection
- Abnormal weight loss
- Decreased blood counts (red or white blood cells)
- Increased liver enzymes in the blood

It is possible that you may have an allergic reaction to the ring. Symptoms of an allergic reaction include rash or other skin irritation, itching, pain in your joints, or difficulty in breathing.

With any product inserted vaginally, it is possible you could experience toxic shock syndrome. Toxic shock syndrome is a rare but serious illness caused by poisons (toxins) released by some types of *Staphylococcus aureus*, a common bacteria. The likelihood of this occurring is rare.

**Risks of anoscope rectal exams**

During collection of rectal fluid samples, insertion of a lubricated anoscope will likely cause mild discomfort or pressure in the rectum or anorectal area. There is the risk of

mild discomfort in addition to a slight risk of bleeding with the insertion of rectal swabs or sponges.

**Other Possible Risks**
You may become embarrassed and/or worried when discussing your sexual practices, alcohol and drug use, ways to protect against HIV and other STIs, 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. Reports via computer will be stored in computers that are password-protected and will not include personal information that could identify or link information to you; only your study ID number will be recorded.

If you are selected for an in-depth interview, the interview will be audio recorded and questions of a personal nature may be asked. Responding to these questions may make you uncomfortable. The audio files will be put into writing by the person interviewing you or by another person who does not know you and does not have your personal information. You should NOT identify anyone in the interviews and any names that might be mentioned on the recording will only be noted in the transcript using a generic description. The audio files will be stored in computers that are password-protected.

It is possible that your involvement in the study could become known to others, and that social harms may result (i.e., because others may think you are 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, communities, and/or employer(s). Finding out your HIV or STI status could cause depression, suicidal thoughts and/or problems between you and your partner. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

**Pregnancy and Breastfeeding**
The DPV VR is not birth control. We do not know what effect DPV has on pregnancy, including the effect of DPV on the fetuses of women who use the VR when pregnant, or the babies of women who use the VR when breastfeeding. Because of this, anyone who is pregnant or breastfeeding may not join this study. Participants who join the study must agree to use an acceptable method of contraception (see Screening Visit for details). Participants who join this study will have pregnancy tests while in the study.

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 you will stop using) the study VR 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. If you become pregnant and you deliver a baby from that pregnancy, we will contact you approximately one year after your delivery to collect information about the health of your baby. ***[SITE TO INCLUDE/AMEND THE FOLLOWING]:*** We will also contact you about a study that collects information about pregnancy and babies up to one year old.

**If You Become Infected with HIV**

The study drug does not cause HIV. However, there is always a chance that through sexual activity or other activities that 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 VR. If HIV infection is confirmed, you will stop your participation in this study.

There is a risk that you may become resistant to DPV by participating in this study. This means you may be unable to be treated with DPV should you become HIV infected in the future.

**BENEFITS**

A 25 mg DPV VR was recently shown in two large studies to help prevent HIV, so participants assigned to this group may experience this benefit. But, we do not yet know if the VRs with 100 mg or 200 mg help prevent HIV. Though 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 HIV/STI risk reduction counseling, HIV and STI testing, physical examinations, pelvic examinations, and routine laboratory testing, including tests to check the overall health of your blood and liver.

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

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 VR may be causing bad effects, you will be told about this. You will also be told when the 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, US Office for Human Research Protections (OHRP), IPM (the nonprofit organization that supplies the VRs), 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.
- You report the use of the following prohibited medications:
    - post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP)
    - Anticoagulants (e.g., heparin, Lovenox, warfarin, Plavix)
- Study staff decide that using the VR would be harmful to you, for example, if you have a bad reaction to the study ring.
- Other reasons that may prevent you from completing the study successfully, such as inability to consistently keep appointments or to stop using prohibited medications or engaging in prohibited practices.

If study staff ask you to stop using the VR, you will be asked to complete an interim visit during which time the procedures highlighted to occur at Visit 10 will be completed. Thereafter, you will continue your regular clinic visit schedule with modified procedures, unless otherwise informed by study staff.

In the event that you are removed from or choose to leave this study, you will be asked to return your VR and complete a final evaluation. If you do not have the VR 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]***

**ALTERNATIVES TO PARTICIPATION**

Researchers are continuing to study DPV to learn more about how it works in humans to protect against HIV infection. There are two currently available methods to prevent sexually transmitted HIV: condom use during sex and/or the use of daily oral Truvada® for pre-exposure prophylaxis (PrEP). PrEP is a new HIV prevention method where people who do not have HIV take an oral tablet every day to reduce their risk of becoming infected. Study staff can provide you with additional information about PrEP if you are interested in learning more.

***[SITES TO INCLUDE/AMEND THE FOLLOWING, IF APPLICABLE]:*** There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing and birth control. We will tell you about those places if you wish.

If you choose not to take part in this study, it will have no effect on the regular medical care that is available to you at this clinic or elsewhere.

**COSTS TO YOU**

***[SITE TO COMPLETE ACCORDING TO SITE CAPACITY]:*** There is no cost to you for study related visits, the VR, physical/pelvic examinations, laboratory tests or other procedures. Treatments available to you from the study site for HIV/STIs 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. If chosen to take part in the in-depth interview, you will receive ***[SITE TO INSERT AMOUNT $XX]***. You may receive ***[SITE TO INSERT AMOUNT $XX]*** for any visits which occur in between your normally scheduled visits.

**CONFIDENTIALITY**

Any information about you obtained from this research will be kept as private as possible. All records related to your involvement in this research study will be kept in a [***SITES TO INSERT***]. Your identity on these records will be indicated by a number rather than by your name, and the information linking these numbers with your name will be kept separate from the research records.

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 FDA, US OHRP, NIH, 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 IRBs or Ethics Committees.
- Study staff.

***[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 STIs 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 or elder 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. 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.

**CLINICALTRIALS.GOV**
A description of this clinical trial will be available on **http://www.ClinicalTrials.gov.** This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

**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 urine, blood, cervical tissue, or vaginal and cervical fluid 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, such as future research to fight HIV and other related diseases. 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, and there is no time limit on how long these samples will be stored. However, 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. Samples may be used by the MTN Laboratory Center to complete additional quality assurance testing, ensuring that laboratory tests work correctly and supply accurate data. It is important that you know that any future testing or studies beyond that 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.

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

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