MTN-024/IPM 031

Phase 2a Safety Study of a Vaginal Matrix Ring Containing Dapivirine in a Postmenopausal Female Population

Microbicide Trials Network

Funding Agencies:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
AUC	area under the curve
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
BV	bacterial vaginosis
CASI	computer assisted self-interview
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CORE	Coordinating and Operations Center
CRF	case report form
CROI	Conference on Retroviruses and Opportunistic Infections
CRS	clinical research site
CT	*Chlamydia trachomatis,* chlamydia
CTA	Clinical Trial Agreement
CVL	Cervicovaginal lavage
CWG	Community Working Group
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAPY	di-amino-pyrimidine
DLV	delavirdine
DNA	deoxyribonucleic acid
EAE	expedited adverse event
ENR	Enrollment
FDA	(US) Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
FSH	follicle-stimulating hormone
g	grams
GC	*Neisseria gonorrhoeae,* gonorrhea
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
hCG	human chorionic gonadotropin
HEC	hydroxyethylcellulose
HIV	Human Immunodeficiency Virus
hu-PBL	human peripheral blood lymphocytes
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	informed consent forms

IRB	Institutional Review Board
IND	Investigational New Drug
IPM	International Partnership for Microbicides
IoR	Investigator of Record
KOH	potassium hydroxide
kg	kilogram
LLOQ	lower limit of quantification
µg	microgram
mg	milligram
mL	milliliter
MTN	Microbicide Trials Network
ng	nanogram
NAAT	nucleic acid amplification test
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
NL	network laboratory
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no-observed-adverse-effect-level
NVP	nevirapine
OHRP	Office for Human Research Protections
PEP	post-exposure prophylaxis
PPD	Pharmaceutical Product Development
PK	pharmacokinetics
PoR	Pharmacist of Record
PrEP	Pre-exposure prophylaxis
PRO	Protocol Registration Office
PSRT	Protocol Safety Review Team
PTID	participant identification
RSC	Regulatory Support Center
RE	Regulatory Entity
RT	reverse transcriptase
RTI	reproductive tract infection
SAE	serious adverse event
SCR	Screening
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SOP	standard operating procedure
SUSARs	Suspected, unexpected serious adverse reactions
SSP	study specific procedures
STI	sexually transmitted infection
TEAE	treatment-emergent adverse events
UA	urinalysis
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
w/w	weight/weight

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MTN-024/IPM 031

Phase 2a Safety Study of a Vaginal Matrix Ring Containing Dapivirine in a Postmenopausal Female Population

INVESTIGATOR SIGNATURE FORM
Version 1.0

March 21, 2013

A Study of the Microbicide Trials Network

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

IND Holder:
International Partnership for Microbicides (IPM)

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

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

_____
Name of Investigator of Record

_____ _____
Signature of Investigator of Record Date

MTN-024/IPM 031

Phase 2a Safety Study of a Vaginal Matrix Ring Containing Dapivirine in a Postmenopausal Female Population

PROTOCOL SUMMARY

Short Title: Study of Dapivirine Vaginal Ring (VR) in a Postmenopausal Female Population

Clinical Phase: Phase 2a

IND Sponsor: IPM

Protocol Chair: Beatrice A. Chen, MD, MPH

Sample Size: Approximately 96 participants

Study Population: Healthy, HIV-uninfected, postmenopausal females, 45-65 (inclusive) years old

Study Sites: Sites selected by MTN leadership

Study Design: Phase 2a, two-arm, placebo-controlled, double-blinded, multi-site, randomized trial (3:1)

Study Duration: Accrual will require approximately 12 months. Each enrolled participant will be followed for approximately 13 weeks.

Study Products:

- Dapivirine VR
- Placebo VR

Study Regimen:

- Participants will be randomized in a 3:1 ratio to receive either a silicone elastomer VR containing 25 mg of dapivirine or a placebo VR; inserted once every 4 weeks for a total of 12 weeks of product use

Primary Objective:

Safety

- To assess the safety of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring in HIV-uninfected postmenopausal women, when inserted once every 4 weeks during 12 weeks of study product use

Primary Endpoints:

Safety

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

- Grade 3 or higher adverse events as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009)

Secondary Objectives:

Acceptability

- To evaluate acceptability of study VR expressed as women's preference for the VR compared to other HIV prevention methods in HIV-uninfected postmenopausal women, when inserted once every 4 weeks during the 12 week study product use period

Adherence

- To evaluate the adherence to a 4-week regimen of dapivirine VR as compared to placebo VR over 12 weeks of use

Pharmacokinetics

- To evaluate the local and systemic dapivirine exposure

Secondary Endpoints:

Acceptability

- The proportion of participants who find the study VR to be as acceptable as other HIV prevention methods

Adherence

- Adherence measures of daily study product use based on self-report over the study product use period

Pharmacokinetics

- Assessments of dapivirine concentrations in plasma, vaginal fluid and cervical tissue

Exploratory Objectives:

Acceptability

- To explore the multi-dimensional aspects of study VR acceptability in HIV-uninfected postmenopausal women after 12 weeks of use

Adherence

- To assess the correlation of dapivirine concentrations and adherence measures

Vaginal Microenvironment

- To describe the genital microenvironment in HIV-uninfected postmenopausal women during 12 weeks of study product use

Exploratory Endpoints:

Acceptability

- Participant's self-report on multiple components of acceptability via attitudinal questions

Adherence

- Residual amount of dapivirine measured in returned VRs
- Dapivirine concentrations in plasma, vaginal fluid, and cervical tissue

Vaginal Microenvironment

- Changes in pH, microflora and biomarkers

Note: Cervical tissue will be collected on a subset of participants taking part in the Cervical Biopsy/ Vaginal Fluid Subsets

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Phase 2a Safety Study of a Vaginal Matrix Ring Containing Dapivirine in a Postmenopausal Female Population
Protocol Number:	MTN-024/IPM 031
Short Title:	Study of Dapivirine Vaginal Ring (VR) in a Postmenopausal Female Population
Date:	March 21, 2013

1.2 Funding Agencies, Sponsor and Monitor Identification

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2 INTRODUCTION

2.1 Postmenopausal Women and the Need for an Effective HIV/AIDS Prevention Option

According to United Nations Programme on Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) (UNAIDS) estimates, 33.3 million people were living with HIV at the end of 2009.[1] In the United States in 2007, 15% of all new HIV infections were among people aged 50 years and older.[2] It is estimated that by 2015, 50% of all individuals living with HIV/AIDS in the United States (US) will be 50 years of age or older[3], consequently, it is not surprising that the rate of the heterosexually acquired HIV infections in older US women is on the rise. In 2004, 6.8% more women between the ages of 50-59 were diagnosed with HIV than in 1999.[4] Persons over the age of 50 may have many of the same extrinsic risk factors for HIV infection as younger persons, including being sexually active, injection drug use, etc., however recent data suggest that postmenopausal women may be at a higher biological HIV risk than premenopausal women.[5]

These data underscore the need to identify a safe and effective HIV prevention delivery system that is appropriate for a postmenopausal woman. Vaginal rings (VR) with the capacity to release drug(s) over a prolonged period of time represent one strategy that may decrease user lapses in adherence. Additionally, these devices have the capacity to release more than one drug at a time which may increase their efficacy and reduce the risk of drug resistance through the increased genetic barrier for viruses exposed to antiretroviral (ARV) drug combinations.

The International Partnership for Microbicides (IPM) has joined with the Microbicide Trials Network (MTN) to evaluate the safety of dapivirine VR in a postmenopausal population, a study product which is currently being tested in two pivotal Phase 3 efficacy trials enrolling women aged 18-45.

2.2 Dapivirine Vaginal Ring

2.2.1 Description

Dapivirine, a non-nucleoside reverse-transcriptase inhibitor (NNRTI), is a substituted di-amino-pyrimidine (DAPY) derivative with potent antiviral activity against HIV-1. Dapivirine is chemically described as 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile.[6] The dapivirine matrix VR is a flexible ring containing 25 mg of drug substance dispersed in a platinum-catalyzed-cured silicone matrix. Dapivirine is known to be well-suited for delivery via VR, as evidenced by favorable safety and pharmacokinetic data to date described below.

Dapivirine was originally developed by Tibotec Pharmaceuticals (Titusville, NJ) as an oral ARV compound and was tested in Phase 1 and 2 clinical trials in more than 200

participants.[7] Although first conceived as an oral therapeutic, dapivirine became a promising topical microbicide candidate due to its proven *in vitro* and *in vivo* efficacy and favorable safety profile as well as its physical and chemical properties. Dapivirine has potent activity against wild-type HIV-1 strains and strains harboring different resistance-inducing mutations. Dapivirine's ARV profile is superior to that of several other NNRTI drugs, including nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). Like other NNRTIs, *in vitro* tests have also shown that dapivirine is not active against HIV-2 and has little or no activity against common sexually transmitted infections (STI). It is therefore not intended for use against HIV-2 or other STIs. Dapivirine does not have any contraceptive properties.[8] Detailed information on dapivirine is available in the Dapivirine VR Investigator's Brochure (IB).[9]

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

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

Summaries of the safety and tolerability of dapivirine as evaluated by IPM and Tibotec Pharmaceuticals in both animal and human studies via the oral and vaginal routes can be found below.

2.2.2 Mechanism of Action

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

2.2.3 Strength of Study Product

The dapivirine VR (Ring-004) will contain 25 mg of dapivirine. Ring-004 is a dapivirine matrix VR containing 25 mg of drug substance dispersed in a platinum-catalyzed-cured silicone matrix.

2.3 Placebo VR

2.3.1 Description

The placebo VR is a flexible, platinum-catalyzed-cured silicone matrix ring, identical to dapivirine Ring-004, containing no active drug.

2.3.2 Mechanism of Action

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

2.3.3 Strength of Study Product

The placebo VR contains no active drug.

2.4 Nonclinical Studies of Dapivirine

2.4.1 *In vitro* Studies of Dapivirine

Anti-HIV-1 Activity

The activity of dapivirine against wild-type (wt) HIV-1, African isolates of HIV-1 (including subtype C virus), and a panel of NNRTI-resistant viruses has been established using *in vitro* models, with 50% effective concentration (EC_{50}) values ranging from 0.3 ng/mL (0.9 nM) against laboratory isolates to <33 ng/mL (<100 nM) for HIV-1 isolates encoding one or more known NNRTI resistance mutations.[6, 10]

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

Resistance

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

systemic concentrations observed in the first clinical trial of one formulation of topical dapivirine (Gel-001).

In the first experiment, population sequencing performed following prolonged exposure of HIV-1_{LAI}-infected MT4 cells to low concentrations of dapivirine for a period of approximately 30 days identified several NNRTI resistance-associated mutations, including Y181C, at dapivirine concentrations of 10 nM and 100 nM, but not at 1 nM and 0.1 nM concentrations. However, both Y181C and V179I were detected when single viral genomes were analyzed by end-point dilution at 1 and 0.1 nM concentrations. The frequency of Y181C was 10-12% both at 1 and 0.1 nM.

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

The significance of Y181C in a single clone at 0.01 nM in the 31-day culture is not clear. It is possible that the sensitive single genome sequencing technology detected some of the pre-existing natural variants present in a virus population in the absence of selective pressure. It was concluded that prolonged exposure to low concentrations of dapivirine can result in selection of viruses carrying NNRTI resistance-associated mutations, but the clinical relevance of these *in vitro* data is not known.[6]

Experiments comparing the selection of resistant viruses following exposure to dapivirine with that following exposure to the NNRTIs UC781, MIV-160, nevirapine and efavirenz, showed that dapivirine demonstrated a high genetic barrier to resistance development in three viral isolates from subtypes B, C, and CRF02_AG. Fully resistant viruses took 12 weeks to emerge, whereas reduced susceptibility to the NNRTIs UC781, efavirenz and nevirapine was detected within 5 weeks. Unlike UC781 and MIV-160, dapivirine did not select for mutations common to all three isolates, although the subtype C VI829 and CRF02_AG MP568 viruses contained the mutations L100I and E138K. Other mutations selected under dapivirine pressure included E138Q, K101E, V108I, K103N, Y181C, V179M/E and F227Y.

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

Cross-resistance

In comparison with NVP, DLV, EFV and emivirine, dapivirine showed significantly better *in vitro* activity against laboratory and recombinant HIV strains resistant to one or more drugs of the same class. The EC_{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 dapivirine, dapivirine was able to inhibit 46% (202/433) of the samples including 41% (142/350) of the strains resistant to EFV. In contrast, only 10% (24/231) of the dapivirine-resistant strains were inhibited by EFV.[6]

2.4.2 Condom Compatibility Studies of Dapivirine

Condom compatibility studies have not been conducted with the VR; however, chemical compatibility studies with different dapivirine-containing gel formulations were conducted on the following types of condoms: [9]

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

The results of condom compatibility testing indicate that dapivirine-containing vaginal gel formulations (0.05%) have no deleterious effects on the integrity of male or female condoms, as indicated by tensile condom properties tested pre- and post-treatment.

2.5 Animal Studies of Dapivirine

Pharmacokinetics

Systemic exposure to dapivirine was low following vaginal administration of dapivirine gels to rabbits.[6] Much higher systemic exposures were obtained in single-dose oral and subcutaneous toxicity studies in mice and rats, and in repeat dose oral toxicity studies in rats, dogs and monkeys. The free fraction of dapivirine in plasma was 0.19-0.34% in the male rat, 0.18-0.39% in the female rat, 0.21-0.22% in the dog and 0.15% in humans. In rats, tissue-to-plasma area under plasma concentration-time curve (AUC_{0-24}) ratios following a single oral dose were 11 in liver, 7-8 in lung, kidney and adrenals, about 4 in spleen and lymph nodes, and 2-3 in brain, heart and muscle. Plasma/tissue equilibrium was rapid, and there was no undue retention of dapivirine in tissues. Following a single oral or vaginal dose of ^{14}C-dapivirine, absorption and distribution of drug-related material to the tissues was moderate in non-pregnant and slow in pregnant female rats. Vaginal gel dosing did not result in greater distribution to the reproductive tissues (except the vaginal wall) than oral dosing. For virtually all tissues, maximal concentrations after vaginal dosing were <1% of those after oral dosing. Drug-related material was shown to freely cross the placenta to the fetus. In dogs, dapivirine concentrations following oral administration for 14 days were about 9 times higher in

liver and muscle, and about 5 times higher in lymph nodes and brain than in plasma. Preliminary metabolism studies demonstrated the presence of free and conjugated metabolites in rats, dogs, monkeys and humans, but the molecular structures have not been elucidated. There was evidence of extensive cytochrome P450 (particularly CYP3A4) mediated metabolism.[6]

Toxicology

The toxicity of dapivirine has been evaluated in a comprehensive program of preclinical studies.[9] These are described in the IB and included repeat dose vaginal toxicity studies in rabbits using gel formulations of dapivirine at concentrations up to 20 mg/mL for 14 days, up to 5 mg/mL for 13 weeks or up to 2 mg/mL for 39 weeks (dose volume = 1 mL/day) in which no local or systemic toxicity was identified.[17] In addition, studies of up to 26 weeks duration were completed in rats and dogs via the oral route. The no-observed-adverse-effect-level (NOAEL) in both species following oral administration was 20 mg/kg/day. C_{max} at the NOAEL was 0.39 µg/mL in rats and 1.21 µg/mL in dogs, which was more than 990 and 3000 times, respectively, the maximum mean plasma concentration (0. 392 ng/mL) in women using a dapivirine ring (Ring-004) for 28 days. AUC at the NOAEL was 4.80 µg.h/mL in rats and 12.98 µg.h/mL in dogs, which is over 570 and 1500 times, respectively, the mean AUC (8.379.ng.h/mL) in women using Ring-004 for 28 days.

Mutagenesis

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

Reproductive Toxicity

In rats, some effects on the developing fetus were observed following oral administration at maternally toxic doses (80 and 320 mg/kg) of dapivirine.[9] However, there were no effects in rats at the maternally non-toxic dose of 20 mg/kg/day, or in rabbits at up to 90 mg/kg. No toxicity to maternal animals or the developing embryo/fetus was seen following vaginal dosing in embryo-fetal development studies in rats (up to 3.3 mg/mL using a dose volume of 0.2 mL/kg) and rabbits (up to 2 mg/mL using a dose volume of 1.0 mL).

Vaginal reproductive toxicity studies in rats and rabbits using a formulation of dapivirine gel (Gel-001) at nominal concentrations up to 3.3 mg/mL (10 mM) or another formulation of dapivirine gel (Gel-002) at up to 2.0 mg/mL (0.2%) did not identify any adverse effects on the maternal animals or the developing embryo/fetus.[9]

Effectiveness

Dapivirine blocked vaginal transmission of HIV-1 in a hu-SCID mouse model in which animals received a single vaginal application of dapivirine gel (candidate research gels containing either Carbopol 940 or hydroxyethylcellulose (HEC)) prior to a non-invasive vaginal challenge with human peripheral blood lymphocytes (hu-PBL) previously

infected *in vitro* with CCR5-tropic and dual tropic (CCR5/CXCR4) HIV-1 strains.[10] Dapivirine prevented a systemic infection with either CCR5 or CCR5/CXCR4 virus strains at concentrations of 2.25 µM (0.7 µg/mL) and higher. The efficacy rate ranged from approximately 70 to 100%, depending on the vaginal gel formulation. The protection resulted directly from the ARV activity of dapivirine, since placebo gels failed to protect and since dapivirine did not show toxicity using mock-infected hu-PBL. Results were better with gels of lower viscosity, probably reflecting the ease with which the vaginal gel was applied to the vagina and thus either the uniformity of distribution over the entire vagina/cervix or the non-traumatic application of the vaginal gel.

2.6 Clinical Studies

2.6.1 Clinical Studies of Dapivirine Vaginal Rings

To date, 26 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted: seven trials of dapivirine VRs (25 mg and 200 mg loads) in which 234 participants were assigned to dapivirine VRs, eight trials of dapivirine vaginal gel in which 491 participants used dapivirine vaginal gel, and 11 trials of oral dapivirine among 211 participants.[6]

Pharmacokinetics

Dapivirine vaginal rings

IPM conducted a 28-day safety and pharmacokinetics (PK) trial (IPM 018) in HIV-uninfected women using tin-catalyzed silicone matrix and reservoir rings containing 25 mg of dapivirine. The rings were found to be generally safe and well-tolerated with a promising drug release profile.[11]

IPM also conducted a 28-day trial (IPM 024) involving 16 healthy, HIV-uninfected, sexually abstinent women, between 18 and 40 years of age. The women were randomly assigned (1:1) to a dapivirine (25 mg) matrix ring or a placebo ring for 28 consecutive days. Post-ring insertion (1.5 hour), quantifiable plasma dapivirine concentrations (lower limit of quantification (LLOQ) = 3.00 pg/mL) were observed.[12] These concentrations showed a gradual increase over time, reaching a mean C_{max} of 355.0 pg/mL by Day 7 (median T_{max}).

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

For dapivirine in vaginal fluids quantifiable concentrations (LLOQ = 0.40 ng) were also observed 1.5 hours after ring insertion. Generally, maximum concentrations were reached earlier than in plasma. The highest concentrations were observed in the area near where the ring was placed (mean C_{max}: 79.9 µg/g; median T_{max}: Day 3), followed by the cervix (mean C_{max}: 66.6 µg/g; median T_{max}: Day 4). Dapivirine vaginal fluid concentrations were well above the reported *in vitro* IC_{50} (50% inhibitory concentration for virus replication) of 0.3 ng/mL in MT4 T cells and the concentration at which greater than 99% inhibition of integrated provirus was observed (3.3 ng/mL) in cervical tissue.

On Day 28, prior to ring removal, the mean concentrations ($C_{pre\text{-}ring\ removal}$) 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 introitus, respectively.[10]

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

IPM 013 was a Phase 1, randomized, double-blind, placebo-controlled trial conducted over three months in 48 healthy, HIV-negative, sexually active women, 18 to 40 years of age in Belgium. This trial evaluated the delivery of dapivirine from the same ring as used in IPM 024, but over different periods of use and assessed local and systemic safety. Participants were randomized (3:1) to either active or placebo ring. Two groups completed the trial with varying lengths of use. In Group A, the VR was removed on Day 28, and a new ring was inserted on Day 31 for 28 days in Group A. In Group B, the initial ring was removed on Day 35 and a new ring was inserted on Day 38 for 21 days. Group B had a third ring inserted on Day 59; this ring was worn for 24 hours.

Compared to vaginal fluids, systemic exposure to dapivirine in plasma was low.[12] Plasma concentrations did not exceed 553 pg/mL, while the highest vaginal fluid concentration obtained was 171 µg/g. Data suggest that dapivirine is readily released from the ring and absorbed into the surrounding tissue and into the bloodstream. Concentrations of dapivirine collected within 4 hours of first ring insertion showed quantifiable plasma (LLOQ = 3.00 pg/mL) and cervicovaginal fluid (LLOQ = 0.4 ng) levels. Interestingly, extending the period the ring was worn from 28 to 35 days resulted in some reductions in cervicovaginal 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 introitus (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 following challenge with HIV-1BaL.

Safety

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

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

Trial Details			Number of Participants				
Trial Number	**Description**	**Country**	**Ring-001 reservoir (200 mg)**	**Ring-002 reservoir (25 mg)**	**Ring-003 matrix* (25mg)**	**Ring-004 matrix** (25mg)**	**Placebo Ring**
IPM 015	Safety and PK in women; 84 days	Multiple Countries in Sub-Saharan Africa	--	--	--	140	140
IPM 018	Safety and PK in women; 28 days	Belgium	--	8	8	--	8
IPM 024	Safety and PK in women; 28 days	Belgium	--	--	--	8	8
MTN-013/IPM 026	Safety and PK in women	United States	--	--	--	12	12
TOTAL participants			**12**	**18**	**8**	**196**	**195**

*Tin-catalyzed matrix ring.
**Platinum-catalyzed matrix ring

Across all clinical trials with multiple ring configurations in healthy participants, the dapivirine VR was generally safe and well-tolerated.[10] IPM has conducted a review of aggregate safety information which identifies vaginal candidiasis as a possible adverse drug reaction caused by dapivirine vaginal ring use.

The first dapivirine VR tested in humans, Ring-001, consisted of two reservoir cores containing a total of 200 mg dapivirine surrounded by a controlled-release outer sheath of silicone elastomer. Ring-001 was tested in a Phase 1, open-label, crossover trial in 12 healthy, sexually abstinent, HIV-uninfected women at a single research center in Belgium (IPM 001).[11] Women used the placebo ring for 7 days followed by the dapivirine ring for 7 days. There were no serious adverse events (SAEs) during the trial and few treatment-emergent adverse events (TEAEs). The dapivirine ring was considered to be safe based on the results of this trial in healthy participants.

Ring-002, a similar formulation with a single dapivirine reservoir core containing 25 mg dapivirine, was tested in a Phase 1, randomized, placebo-controlled trial conducted at a single research center in Belgium (IPM 008).[13] Ten women underwent 7-day exposure to dapivirine Ring-002, and three women used a placebo ring for 7 days. There were no SAEs during the trial and few TEAEs. The trial results showed that the dapivirine ring was safe in healthy participants.

Ring-003, a dapivirine matrix VR containing 25 mg of drug substance dispersed in a tin-catalyzed-cured silicone matrix, was compared with Ring-002 in a Phase 1, randomized, placebo-controlled trial conducted at a single research center in Belgium (IPM 018). Twenty-four healthy, HIV-uninfected women, 18 to 35 years of age, were randomly assigned (1:1:1) to dapivirine matrix ring, dapivirine reservoir ring, or placebo ring for 28 consecutive days. No SAEs were reported during the study. No TEAEs

were assessed by the investigator as definitely or probably related to the ring, and similar percentages of participants in the dapivirine and placebo ring groups had TEAEs considered to be possibly related to the ring.

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

IPM 015, a double-blind, randomized, placebo-controlled Phase 1/2 trial in 280 healthy, HIV-negative women who, inserted a vaginal ring once every 21-35 days over a 12-week period. Five serious AEs were reported, one occurring in the dapivirine ring arm.[14] None of the SAEs were judged to be related to product. No TEAEs led to premature discontinuation of ring use.

IPM 015 was a Phase I/II trial designed to assess and compare the safety of a dapivirine vaginal ring against a placebo vaginal ring when inserted once every 28 days over a 12-week period among healthy, HIV-negative women. Five SAEs occurred during the trial, of which four occurred in placebo participants. One participant in the dapivirine treatment group reported Grade 3 tonsillitis, which was unrelated to the investigational product. Four participants in the placebo treatment group reported one instance each of bronchiectasis (Grade 3), peritonsillar abscess (Grade 3), suicide attempt (Grade 3), and hemopneumothorax (Grade 4). The hemopneumothorax was caused by a physical assault; this event was unrelated to the investigational product. A chemical pregnancy was reported for one participant in the placebo ring group who discontinued product use, but continued to attend the research center for safety evaluations and completed the remainder of trial visits. Apart from the latter two events, none of the SAEs or TEAEs led to premature discontinuation of ring use.

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

MTN-013/IPM 026, a Phase 1 safety and pharmacokinetics study of dapivirine VR, maraviroc VR, dapivirine/maraviroc VR and placebo VR, enrolled approximately 48 women between the ages of 18-40. The participants were randomized in a 1:1:1:1 ratio to 28 days of continuous study vaginal ring use. Over the course of 52 days, 14 follow-up visits occurred. Safety and intensive PK assessments were conducted on all participants. Safety comparisons of each product to placebo as well as data related to absorption and distribution is anticipated to be available in the first quarter of 2013.

In March of 2012, The Ring Study, also known as IPM 027, was initiated. IPM 027 is a randomized, double-blind, placebo-controlled efficacy and long-term safety study that will enroll 1,650 healthy, HIV-uninfected women, ages 18-45. The study is being conducted at several sites in sub-Saharan Africa. Study participants will use either the dapivirine ring or the placebo ring every four weeks over approximately two years. The main goals of The Ring Study are to evaluate the long-term safety and efficacy of the dapivirine ring for the prevention of HIV-1 as compared to a placebo ring, when used by healthy, HIV-negative women over a two-year period. Additional goals include measuring the incidence of curable STIs, HIV-2 and pregnancy; monitoring ring acceptability (how well women like using the ring) and adherence (if women use the ring as intended) as reported by the study participants; and tracking the development of any HIV-1 drug resistance in participants who become HIV positive during the study. The study is anticipated to conclude in 2015.

MTN-020, A Study to Prevent Infection with a Ring for Extended Use or ASPIRE, is a Phase 3 clinical trial designed to assess the effectiveness and safety of a ring containing 25 mg of dapivirine for the prevention of HIV acquisition in women. The double-blind, randomized controlled trial is being conducted in HIV-uninfected women, between the ages 18 – 45, in multiple sites across sub-Saharan Africa. In August of 2012, ASPIRE initiated the enrollment of 3476 participants. The study is anticipated to conclude in 2015.

2.6.2 Clinical Studies of Placebo VR

Similar placebo VRs (Ring-004 with no active ingredient) were studied in IPM 024, IPM 013, IPM 015 and MTN-013/IPM 026.

2.7 Behavioral Studies

2.7.1 Acceptability of Dapivirine Vaginal Ring

IPM 011 assessed the acceptability of the vaginal rings of the candidate microbicide dapivirine VR, and the placebo VR. The study participants found the ring to be very comfortable (95%), very easy to insert (94%) and remove (92%), and rarely were the rings felt during daily activities. All questionnaire respondents, when asked if they would be willing to use the vaginal ring if shown to be effective for HIV prevention, replied that they would use the VR.[15]

In IPM 015, at Week 12, 97% of women found the dapivirine VR to be comfortable and were willing to use the ring if it was found to be effective. Women preferred to wear the ring every day (97%) and reported that the ring did not interfere with their daily activities (89%).[14] In terms of the male partner acceptability, 63% of women reported that their partner did not feel the ring during sex. Of those participants who reported that their partner felt the ring, only 1% reported that this might be or definitely was a problem.[14]

2.7.2 Adherence of Dapivirine Vaginal Ring

In IPM 011, 11% of the women experienced expulsions, with the most common reason for expulsion/removal being 'menses related'. In the majority of cases (64%), the ring was washed and re-inserted.[15]

In IPM 015, perfect adherence was reported by 92% of the female participants. Perfect adherence was defined as never having the ring out for more than an entire day. Of the women who reported that the ring was out, the most common activity for expulsion was urination/defecation. The most common reason reported by participants for ring removal was cleaning. As the study progressed, more women reported removing the ring for sexual intercourse, 17% at week 2 and 36% by week 12.[14]

2.8 Study Hypotheses and Rationale for Study Design

2.8.1 Study Hypotheses

MTN-024/IPM 031 hypothesizes that the dapivirine VR will be safe and well-tolerated for once-monthly use among healthy, postmenopausal females.

2.8.2 Rationale for Study Design

Based on *in vitro*, *in vivo*, and *ex vivo* studies described in the Dapivirine VR IB, dapivirine shows great promise as a topical microbicide to prevent HIV-1 infection.

Vaginal rings have already been developed and approved as delivery methods for medications. For example, NuvaRing®, a contraceptive VR made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate, in which 2.7 mg of ethinyl estradiol and 11.7 mg of etonogestrel are dispersed, has been found to be both effective and acceptable to women. In an acceptability study involving 1,950 NuvaRing® users, 45.5% of women cited that their reason for liking the VR was "not having to remember anything". In a recently completed randomized controlled trial testing two alternative delivery systems for combined hormonal contraceptive, women overwhelmingly preferred the ring to oral contraceptives ($P<.001$).[16] These contraceptive ring data are encouraging as microbicide ring effectiveness will likely correlate with consistent and correct use. It is likely that products that can be applied less frequently will be more acceptable to users, achieve better user-adherence, and may lead to increased effectiveness. Vaginal rings that need only be replaced every 28

days may have benefits over dosage forms that need to be used more frequently, as well as offer a wider choice of microbicide formulations for women if proven effective.

Pfizer (formerly Pharmacia and Upjohn Company) has marketed Estring® (estradiol vaginal ring), a VR that is also made from silicone elastomer and contains estradiol in order to treat local symptoms of urogenital atrophy, since 1993. Prior to the launch of Estring®, the biological safety of the silicone elastomer was studied in various *in vitro* and *in vivo* test models. The results show that the silicone elastomer is non-toxic, non-pyrogenic, non-irritating, and non-sensitizing.[17]

Femring® (estradiol acetate vaginal ring), a hormone replacement product approved in June 2003 by the United States (U.S.) Food and Drug Administration (FDA), treats menopause-induced vasomotor symptoms (e.g., hot flushes) and symptoms of vulvar and vaginal atrophy (e.g., dryness).

Although these rings are not exactly the same as the IPM ring, the extensive clinical trial and post-marketing experience gained from these products provides further assurance of the safety of silicone elastomer rings as vaginal drug delivery devices. An acceptability trial of the silicone elastomer ring used in Femring® (but containing no drug) among postmenopausal women in the U.S. demonstrated very high acceptability and ease of use, encouraging results for our test population.[18, 19] IPM recently evaluated the acceptability and safety of a similar placebo VR in the IPM 011 study (n=170). This study confirmed that the placebo ring was safe and acceptable to users and their male partners.

MTN-024/IPM 031 participants will be randomized in a 3:1 ratio to receive either a silicone elastomer VR containing 25 mg of dapivirine or a placebo VR; inserted once every 4 weeks for a total of 12 weeks of product use on study. Safety data from MTN-013/IPM 024 suggest that AEs will be observed within 5 days of ring removal, thus participants will be followed for 1 week beyond the cessation of study product use to allow for the capture of adverse events. MTN-024/IPM 031 will fill a void in the dapivirine VR research portfolio, by providing the necessary safety data in postmenopausal females, as all clinical trials completed to date have been performed in women younger than 45 years. These data will be added to the efficacy data anticipated from MTN-020 and IPM 027.

2.9 Other Protocol Considerations

Acceptability and Preference Assessment

Understanding postmenopausal women's perceived risk and willingness to incorporate a vaginal ring into their HIV prevention package is critical, however, it is important to first take measure of current uptake of the widely available HIV prevention method for this population, condoms.

Sexual activity continues well beyond a female's reproductive years. If exposed to HIV, this population may be at increased risk of HIV-infection due to biological changes such

as decreased antibody production, vaginal atrophy and decreased lubrication.[20] While data are limited regarding individuals' perceived risk of acquiring sexually transmitted infections and HIV, data is available regarding their condom use. Proper condom use is critically important in this population, as older women are more likely to become infected with HIV through heterosexual intercourse, per episode, as compared to younger women.[21] In a cross-sectional survey of 55 community residing women between the ages of 58-93, 57% of respondents had engaged in sexual activity since their 60th birthday. Of women who had been sexually active in the past ten years, 60% of them did not use a condom.[22] The primary reason for non-use was the perception that condoms are only used for contraception. Older women have also reported that they are less experienced using condoms than their younger counterparts.[23] Women in monogamous or long-term relationships may feel there is no need to request safer sex practices as it may suggest suspicion and uncertainty in a long-term sexual partner.

Of the women who were using condoms, their use of condoms decreased with age.[21]

Low condom use is an important concern as we move into expanding the HIV prevention method mix for women at various ages. MTN-024/IPM 031 participants will provide valuable data on their current HIV prevention preferences and how VRs may fit into the method mix.

3 OBJECTIVES

3.1 Primary Objective

Safety

- To assess the safety of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring in HIV-uninfected postmenopausal women, when inserted once every 4 weeks during 12 weeks of study product use

3.2 Secondary Objectives

Acceptability

- To evaluate acceptability of study VR expressed as women's preference for the VR compared to other HIV prevention methods in HIV-uninfected postmenopausal women, when inserted once every 4 weeks during the 12 week study product use period

Adherence

- To evaluate the adherence to a 4-week regimen of dapivirine VR as compared to placebo VR over 12 weeks of use

Pharmacokinetics

- To evaluate the local and systemic dapivirine exposure

3.3 Exploratory Objectives

Acceptability

- To explore the multi-dimensional aspects of study VR acceptability in HIV-uninfected postmenopausal women after 12 weeks of use

Adherence

- To assess the correlation of dapivirine concentrations and adherence measures

Vaginal Microenvironment

- To describe the genital microenvironment in HIV-uninfected postmenopausal women during 12 weeks of study product use

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-024/IPM 031 is a Phase 2a, two-arm, placebo-controlled, double-blinded, multi-site, randomized trial of dapivirine VR versus placebo VR (a vaginal ring inserted once every 4 weeks for a total of approximately 12 weeks) in healthy, HIV-uninfected, postmenopausal women.

4.2 Summary of Endpoints

Primary Endpoints:

Safety

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

- Grade 3 or higher adverse events as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009)

Secondary Endpoints:

Acceptability

- The proportion of participants who find the study VR to be as acceptable as other HIV prevention methods

Adherence

- Adherence measures of daily study product use based on self-report over the study product use period

Pharmacokinetics

- Assessments of dapivirine concentrations in plasma, vaginal fluid and cervical tissue

Exploratory Endpoints:

Acceptability

- Participant's self-report on multiple components of acceptability via attitudinal questions

Adherence

- Residual amount of dapivirine measured in returned VRs
- Dapivirine concentrations in plasma, vaginal fluid, and cervical tissue

Vaginal Microenvironment

- Changes in pH, microflora and biomarkers

Note: Cervical tissue will be collected on a subset of participants taking part in the Cervical Biopsy/Vaginal Fluid Subsets

4.3 Description of Study Population

The study population will be healthy, HIV-uninfected, postmenopausal women who meet the criteria outlined in Section 5.2 and 5.3.

4.4 Time to Complete Accrual

Accrual is expected to be complete in approximately 12 months.

4.5 Study Groups

Approximately 96 females will be randomized in a 3:1 ratio to one of the following study groups:

- Dapivirine VR
- Placebo VR

4.6 Expected Duration of Participation

The expected trial duration for each enrolled participant is approximately 13 weeks.

4.7 Sites

Sites selected by the MTN leadership will participate in MTN-024/IPM 031.

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 gynecological offices and community-based locations. 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-024/IPM 031, 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-024/IPM 031 retention.

5.2 Inclusion Criteria

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

1) Age 45 through 65 years (inclusive) at Screening, verified per site SOPs

2) Per participant report, postmenopausal at Screening, defined as amenorrheaic for the past 12 months (minimum) or at least 6 months status post-bilateral oophorectomy

3) Follicle-stimulating hormone (FSH) level at 40 mIU/ml or higher at Screening

4) Able and willing to provide written informed consent to be screened for and enrolled in MTN-024/IPM 031

5) Able to communicate in spoken and written English

6) Able and willing to comply with all study procedural requirements

7) Willing to only use study provided and/or approved vaginal products throughout the duration of study participation.

8) Willing to abstain from inserting study approved lubricant into the vagina for 72 hours prior to each visit

9) Willing to abstain from vaginal intercourse for 72 hours prior to each visit

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

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

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

13) Per participant report at Screening and Enrollment, agrees to use male latex condoms for sexual intercourse

14) Per participant report at Screening and Enrollment, states a willingness to refrain from inserting any <u>non-study</u> vaginal products or objects into the vagina including, but not limited to spermicides, female condoms, diaphragms, topical or systemic hormone replacement therapy, including vaginal estrogens, and/or hormonal contraceptives, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), vaginal douches, lubricants and moisturizers, sex toys (vibrators, dildos, etc.), for the duration of the study participation.

    Note: Use of <u>study approved</u> lubricant is permitted.

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

Participants in the biopsy subset must also meet the following criteria at Screening to be eligible for inclusion:

16) Willing to abstain from inserting anything into the vagina for 72 hours following the collection of biopsies, including abstaining from vaginal intercourse

17) Anatomy sufficient for the collection of cervical biopsies

5.3 Exclusion Criteria

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

1) Per participant report at screening:
   a) Plans to relocate away from the study site during study participation
   b) Plans to travel away from the study site for more than 4 consecutive weeks during study participation

2) Pregnant at screening

   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.

3) Diagnosed with urinary tract infection (UTI) at Screening or Enrollment

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

4) Diagnosed with pelvic inflammatory disease, an STI or reproductive tract infection (RTI) requiring treatment per current Centers for Disease Control and Prevention (CDC) guidelines at Screening or Enrollment

   Note: Otherwise eligible participants diagnosed during screening with pelvic inflammatory disease or STI/RTI requiring treatment per CDC guidelines — other than asymptomatic bacterial vaginosis (BV) and asymptomatic candidiasis — are offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 45 days of obtaining informed consent for screening, the participant may be enrolled. Genital warts requiring treatment also must be treated prior to Enrollment. Genital warts requiring therapy are defined as those that cause undue burden or discomfort to the participant, including bulky size, unacceptable appearance, or physical discomfort.

5) Has a clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff) at Screening or Enrollment, as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009), Addendum 1-Female Genital Grading Table for Use in Microbicide Studies

   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 Investigator of Record (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. If improvement to a non-exclusionary grade or resolution is documented within 45 days of providing informed consent for screening, the participant may be enrolled.

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

   a) Known adverse reaction to any of the study products (ever)
   b) Known adverse reaction to latex (ever)
   c) Chronic and/or recurrent vaginal candidiasis
   d) Topical or systemic hormone replacement therapy and/or hormonal contraception within the 6 months prior to Enrollment
   e) Non-therapeutic injection drug use in the 12 months prior to Enrollment
   f) Post-exposure prophylaxis (PEP) for HIV exposure within the 6 months prior to Enrollment
   g) Pre-exposure prophylaxis (PrEP) for HIV prevention within the 6 months prior to Enrollment
   h) Last pregnancy outcome 6 months or less prior to Enrollment
   i) Gynecologic or genital procedure (e.g., tubal ligation, dilation and curettage, piercing) 90 days or less prior to Enrollment
   j) Currently breastfeeding
   k) At Screening, severe pelvic relaxation such that either the vaginal walls or the uterine cervix descend beyond the vaginal introitus with valsalva maneuver
   l) Participation in any other research study involving drugs, medical devices, vaginal products, or vaccines, in the 45 days prior to Enrollment

7) As determined by the IoR/designee, any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease

8) Has any of the following laboratory abnormalities at Screening Visit:
   a) Aspartate aminotransferase (AST) or alanine transaminase (ALT) Grade 1 or higher*
   b) Creatinine Grade 2 or higher*
   c) Hemoglobin Grade 2 or higher*
   d) Platelet count Grade 1 or higher*
   e) Pap result Grade 2 or higher**

   Note: Otherwise eligible participants with an exclusionary test may be re-tested during the screening process.

   Note: Women with a documented normal result within the 12 months prior to Enrollment need not have a Pap smear during the screening period. Women with a Grade 1 abnormal Pap smear can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology). Need for a repeat Pap within 6 months does not preclude Enrollment prior to that result becoming available. If the participant has had a

hysterectomy for reasons not related to cervical dysplasia, a Pap smear need not be performed.

9) 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

*Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009)

**Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the Division of AIDS (DAIDS) Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009)

5.4 Co-enrollment Guidelines

As indicated in Section 5.2, participants must not take part in other research studies involving drugs, medical devices, vaginal products, or vaccines, after the Screening Visit and while taking part in MTN-024/IPM 031 unless approved by the Protocol Safety Review Team (PSRT) and Protocol Chair. Participation in the following types of studies may be allowed at the discretion of the IoR/designee after consultation with the Protocol Chair and PSRT:

- Participants may take part in MTN ancillary studies
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-positive persons
- Participants who become pregnant may take part in observational studies, including pregnancy registries

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-024/IPM 031, 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 two study regimens:

Table 2: Study Regimen

Group	N	Group Description
A	72	Dapivirine VR, containing 25 mg dapivirine
B	24	Placebo VR

Each participant will receive either a VR containing 25 mg dapivirine or a placebo VR. Participants will be randomized in a 3:1 ratio. The VR should be worn for approximately 28 consecutive days at a time but not more than 35 days before being replaced. A new VR will be inserted into the vagina at the Enrollment Visit and at each subsequent monthly visit. The previously inserted ring will be removed by the participant or clinician/designee at each monthly visit. The participant will be followed for approximately 1 week following the final VR removal.

6.2 Administration

The participant will self-insert (or insertion may be performed by clinician/designee, if necessary), the study VR at the Enrollment Visit and each subsequent visit when a VR is dispensed.

Study participants will be given detailed instructions in the clinic on proper VR insertion and removal procedures at the Enrollment Visit and at subsequent follow-up visits. The attempt of these procedures must be documented. Additional details on administration (ring insertion, removal, procedures in the event of expulsion or loss, including cleaning procedures) will be provided in the MTN-024/IPM 031 Study Specific Procedures (SSP) Manual.

6.3 Study Product Formulation

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

6.3.1 Dapivirine VR

Dapivirine 0.3125% (w/w) is dispersed in a flexible, opaque, cured silicone VR delivery device. The VR will contain 25 mg of dapivirine. The dapivirine VR should be stored at 15°C to 30°C.

6.3.2 Placebo VR

The placebo VR is manufactured with the same components as the drug-containing rings, except that it contains USP titanium dioxide dispersed in the silicone fluid as colorant, and no active pharmaceutical ingredient. The purpose of the colorant is for maintaining blinded conditions. The placebo VR should be stored at 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 Study Product Dispensing

Study VRs will be dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. Dispensing will take place on the day of enrollment and at each scheduled follow-up visit, except at the Final Clinic Visit.

6.4.3 Accountability

Each Clinical Research Site (CRS) Pharmacist of Record (PoR) is required to maintain a complete record of all study product received. The procedures to be followed are provided in the MTN-024/IPM 031 Pharmacist Study Product Management Procedures Manual.

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

6.4.4 Retrieval of Study Product

Study product use for a participant may be temporarily held or permanently discontinued. Study product must be retrieved (optimally within 24 hours) and returned to the clinic when product use is permanently discontinued for HIV seroconversion (see table below). Additional study product retrieval specifications in response to product holds, discontinuations for other reasons, or IoR instruction, can be found in Table 3. Study product retrieval may occur either by the participant returning the VR (used) to study staff within the specified timeframe or attempts should be made by study staff to contact the participant and retrieve the study product as soon as possible.

Table 3: Retrieval of Study Product

	Retrieve Study Product
Permanent discontinuation or temporary hold due to potential HIV seroconversion	Within 24 hours
Permanent discontinuation for any other reason or IoR discretion	Within 5 working days
Temporary hold for reasons with expected duration of at least 7 days	Within 7 working days

In addition to the specifications listed above, under any circumstances, if product hold extends for 7 days or more, and product has not been retrieved as of the seventh day, study staff members must make every effort to retrieve study product within 7 additional working days.

It is not necessary to retrieve study products from participants for whom study product use is being temporarily held for less than 7 days. However, study products may be retrieved from such participants, to protect their safety, if there is concern that the participant may not comply with clinic staff instructions to refrain from study product use for the duration of the temporary hold. For all study product holds requiring retrieval of study product(s), if the study product(s) are not retrieved within timeframe stated in Table 3 above, the MTN-024/IPM 031 PSRT must be informed.

If prolonged use (greater than 35 days) of the study VR has occurred, attempts should be made to contact the participant and retrieve the study product as soon as possible.

For each participant, all VRs remaining in the participant's possession should be retrieved at the Final Clinic Visit. If the participant does not bring her remaining study product to this visit, study staff must arrange to retrieve the VR within 2 business days. If the study product(s) are not retrieved within that timeframe, the MTN-024/IPM 031 PSRT must be informed.

6.5 Product Use Instructions

Participants will receive study product use instructions at the Enrollment Visit and at additional follow-up visits, as needed. Site staff will counsel participants in VR product use; including, to refrain from removing the ring (except as directed), and instructions for re-insertion in case of accidental ring expulsion, etc. Additional details will be provided in the MTN-024/IPM 031 SSP Manual. Participants will also be counseled on prohibited practices as described in Section 6.7.

6.6 Concomitant Medications

Enrolled study participants may use concomitant medications during study participation with the exception of medications and products listed as prohibited. All concomitant medications as well as illicit substances reported throughout the course of the study will be recorded 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.

Concomitant medications that either inhibit or induce CYP450 enzymes will be permitted. Systemic exposure to dapivirine observed in women following use of dapivirine ring is very low. Therefore, there is not expected to be a significant change in the dapivirine concentration with concomitant use of CYP450 (including CYP3A4) inducers or inhibitors. The low systemic exposure to dapivirine also suggests that it is very unlikely to induce the metabolism of other co-administered drugs.

6.7 Use of Intravaginal Medications/Products and Practices

All participants will be counseled to avoid the use of non-study vaginal products during study participation. Concomitant use of prohibited non-study vaginal products or other devices including, but not limited to: spermicides, female condoms, diaphragms, topical or systemic hormone replacement treatment, including vaginal estrogens, and/or hormonal contraceptives, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), vaginal douches, lubricants and moisturizers, sex toys (vibrators, dildos, etc.) will be assessed. These products will be recorded on forms designed for that purpose. Participants who report use of these products during study product use periods will be counseled regarding the use of alternative methods and study staff should reference Section 9.3 and 9.4 for temporary hold and/or permanent discontinuation guidelines. Condoms provided by study staff will not be coated with any type of spermicide.

Use of study approved lubricant is permitted, however, participants should abstain from inserting anything into the vagina for 72 hours prior to each clinic visit, including abstaining from the use of study approved lubricant and vaginal intercourse. Participant use of these products, including frequency and amount of study-approved lubricant used, when available, and sexual intercourse will be assessed at each follow-up visit. Visits need not be rescheduled in the event that a participant reports the use of vaginal products or engaging in a coital episode in the previous 72 hours, see the MTN-024/IPM 031 SSP Manual available at www.mtnstopshiv.org.

In addition, participants in the Intensive PK subset should refrain from engaging in vaginal intercourse for 72 hours following the collection of the biopsies.

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 are provided in the MTN-024/IPM 031 SSP Manual available at www.mtnstopshiv.org.

Figure 1: 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. At each site, procedures and documentation will comply with local IRB requirements.

7.2 Screening Visit

A Screening Visit may take place up to 45 days prior to the Enrollment Visit. Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed participant consent 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.

Table 4: Screening Visit

Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent for Screening, Enrollment and Long-Term Storage and Future Testing • Assign participant identification (PTID) • Collect locator information • Collect demographic information • Assess eligibility • Provide reimbursement • Schedule next visit*
Behavioral/Counseling		• Provide counseling o HIV/STI risk reduction o Male condom o HIV pre-and post-test
Clinical		• Obtain medical history • Obtain menstrual history • Obtain concomitant medications • Perform physical examination • Perform pelvic examination • Disclosure of available test results • Treat for UTI/RTI/STI or refer*
Laboratory	**Urine**	• Collect urine for: o Human chorionic gonadotropin (hCG) o Dipstick UA and/or urine culture per local standard of care*
	Blood	• Collect blood for: o Serum chemistries o Complete blood count (CBC) with platelets o HIV-1 serology o Syphilis serology o Follicle-stimulating hormone (FSH)
	Pelvic Samples	• Pelvic Sample Collection o Vaginal swab for rapid Trichomonas test o Vaginal nucleic acid amplification test (NAAT) for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (GC/CT) o Saline wet mount for BV* o Potassium hydroxide (KOH) wet mount for candidiasis* o Pap smear interpretation* o Herpes lesion testing*
Study Product Supply		• Provide study condoms*

*If indicated

7.3 Enrollment Visit (Day 0)

Table 5: Enrollment Visit

Enrollment Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Confirm eligibility • Randomization • Provide reimbursement • Schedule next visit and/or contact
Behavioral/Counseling		• Administer baseline behavioral assessment • Administer product preference/acceptability assessment • Provide counseling o HIV/STI risk reduction o Product adherence o Protocol adherence o HIV pre and post-test* o Male condom*
Clinical		• Review medical history, to include: o Menopausal Rating Scale o Urogenital Distress Inventory (UDI-6 Short Form) • Review/update concomitant medications • Perform physical examination • Perform pelvic examination – Visual inspection per guidelines for naked eye inspection described in the World Health Organization (WHO)/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004 • Disclosure of available test results • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o hCG* o Dipstick UA and/or urine culture, per local standard of care*
	Blood	• Collect blood for: o Plasma archive o HIV-1 serology* o Serum chemistries* o CBC with platelets*
	Pelvic Samples	• Pelvic Sample Collection o Vaginal swab for Gram stain o Vaginal pH o Vaginal swab for quantitative vaginal culture o Cytobrush for flow cytometry Θ o Cervicovaginal lavage (CVL) for biomarkers o Vaginal swabs for biomarkers o Vaginal NAAT GC/CT* o Saline wet mount for BV* o KOH wet mount for candidiasis* o Vaginal swab for rapid Trichomonas test* o Herpes lesion testing*

Enrollment Visit	
Component	**Procedures**
Study Product Supply	• Participants will receive study VR, product use instructions and will be instructed to self-insert the study VR, followed by bimanual exam to check placement • Provide male condoms* • Provide lubricant*

* If indicated, Θ To be collected on participants with appropriate anatomy at selected site(s)
Note: Cervical samples will be collected on women with appropriate anatomy.

7.4 Follow-up Study Visits and Phone Calls

Table 6: 4-Week and 8-Week Study Visits

4-Week and 8-Week Study Visits		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next study visit
Behavioral/Counseling		• Administer behavioral assessment • Administer adherence assessment • Administer product preference/acceptability assessment • Provide counseling o HIV/STI risk reduction o Product adherence o Protocol adherence o HIV pre-and post-test* o Male condom*
Clinical		• Obtain medical history, to include: o Urogenital Distress Inventory (UDI-6 Short Form) • Review/update concomitant medications • Perform targeted physical examination • Perform pelvic examination o Visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004 • Record/update AEs • Disclosure of available test results • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o Dipstick UA and/or urine culture, per local standard of care* o NAAT for GC/CT*
	Blood	• Collect blood for: o PK o HIV-1 serology* o Serum chemistries* o CBC with platelets*
	Samples	• Pelvic Sample Collection o CVL for biomarkers (at 4-week only) o Vaginal swabs for biomarkers (at 4-week only) o Vaginal swab for Gram stain o Vaginal swab for quantitative vaginal culture o Tear test strips for PK on a subset of participants (See Section 7.7) o Vaginal pH o Saline wet mount for BV* o KOH wet mount for candidiasis* o Vaginal swab for rapid Trichomonas test* o Herpes lesion testing*

4-Week and 8-Week Study Visits	
Component	**Procedures**
Study Product Supply	• Participants will receive study VR, product use instructions and will be instructed to self-insert the study VR, followed by bimanual exam to check placement • Collect study product • Provide male condoms* • Provide lubricant*

* If indicated

Table 7: 12-Week Final Clinic Visit/ Early Termination Visit

12-Week Final Clinic Visit/ Early Termination Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next contact

Behavioral/Counseling		• Administer behavioral assessment
		• Administer adherence assessment
		• Administer product preference/acceptability assessment
		• In-depth interview on a subset of participants (See Section 7.8)
		• Provide counseling
		  o HIV pre-and post-test
		  o HIV/STI risk reduction
		  o Male condom*

Clinical		• Review/update medical history, to include:
		  o Menopause Rating Scale
		  o Urogenital Distress Inventory (UDI-6 Short Form)
		• Review/update concomitant medications
		• Perform targeted physical examination
		• Perform pelvic examination
		  o Visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004
		• Record/update AEs
		• Disclosure of available test results
		• Treat for UTIs/RTIs/STIs or refer*

Laboratory	**Urine**	• Collect urine for:
		  o NAAT for GC/CT*
		  o Dipstick UA and/or urine culture, per local standard of care*

	Blood	• Collect blood for:
		  o PK
		  o Serum chemistries
		  o CBC with platelets
		  o HIV-1 serology

12-Week Final Clinic Visit/ Early Termination Visit		
Component		**Procedures**
	Pelvic Samples	• Pelvic Sample Collection o Vaginal swab for Gram stain o Vaginal swab for quantitative vaginal culture o Tear test strip(s) for PK on a subset of participants (See Section 7.7) o Vaginal pH o Vaginal swabs for biomarkers o Cytobrush for flow cytometry Θ o CVL for biomarkers o Cervical biopsies for PK on a subset of participants (Intensive PK) (See Section 7.7) o Saline wet mount for BV* o KOH wet mount for candidiasis* o Vaginal swab for rapid Trichomonas test* o Herpes lesion testing*
Study Product Supply		• Collect study product • Provide male condoms*

* If indicated , Θ To be collected on participants with appropriate anatomy at selected site(s)

7.4.1 Follow-Up Phone Calls: 1-Week, and 13-Week/Study Termination

Study staff will follow-up with participants via phone call one week following the Enrollment Visit and one week following the 12-Week Final Clinic Visit/Early Termination Visit. Study staff will inquire about AEs.

Table 8: 1-Week and 13-Week/Study Termination Follow-Up Phone Calls

Component	Procedures
Administrative and Regulatory	• Provide reimbursement~
Clinical	• Concomitant medications • Record/update AEs

~ Sites to reference SOPs

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

Except in the specific cases mentioned below (see Sections 7.5.1 and 7.5.2), a participant who discontinues study product will be encouraged to remain in the study if they are willing.

7.5.1 Participants Who Become Infected with HIV-1

If a participant becomes infected with HIV-1 after the Enrollment Visit, she will be referred to local care and treatment services and may return to the research clinic for additional counseling and other support services, as needed. Follow-up visits will be discontinued and the participant will be considered terminated from the study. Participants who seroconvert after randomization may be offered additional laboratory testing (such as HIV viral load and HIV drug resistance testing), as clinically indicated per discussion between IoR and NL. Please reference the MTN-024/IPM 031 SSP Manual for additional details (www.mtnstopshiv.org).

7.5.2 Participants Who Become Pregnant

This study will be enrolling postmenopausal women, thus it is extremely unlikely that a participant will become pregnant during this study. In the rare event 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.

Participants who become pregnant while on study product may be offered enrollment in MTN-016 (www.mtnstopshiv.org), provided their study site is taking part in MTN-016.

For additional details about obtaining pregnancy outcome, please reference the MTN-024/IPM 031 SSP (www.msnstopshiv.org).

7.5.3 Participants Who Voluntarily Discontinue Study Product

All protocol-specified study procedures will continue except:

- Provision of study product
- PK specimen collection
- Provision of counseling:
    - Adherence
    - Product use
- Pelvic exams, unless required for AE follow-up

The behavioral assessments will be administered according to guidance from the protocol team.

The aforementioned study procedures will occur at the visit that product is discontinued and then be omitted at subsequent visits. Completion of these procedures will resume if/when study product use is restarted.

7.5.4 Participants Who Are Discontinued from Study Product by the Site Investigator

All protocol-specified study procedures will continue except:

- Provision of study product
- PK specimen collection
- Provision of counseling:
    - Adherence
    - Product use
- Pelvic exams, unless required for AE follow-up

The behavioral assessments will be administered according to guidance from the protocol team.

The aforementioned study procedures will occur at the visit that product is discontinued and then be omitted at subsequent visits. Completion of these procedures will resume if/when study product use is restarted.

7.6 Interim Visits

Interim visits may be performed at any time during the study. All interim contacts and visits will be documented in participants' study records and on CRFs when applicable.

7.7 Pharmacokinetics

The entire MTN-024/IPM 031 cohort will provide plasma for PK at Visits 3, 4 and 5.

A subset of approximately 30 participants across MTN-024/IPM 031 sites will be asked to provide vaginal fluid via tear test strip(s) at Visits 3, 4 and 5. These participants will be asked to opt-in to the PK subset.

An additional 15 participants will be asked to provide vaginal fluid via tear test strip(s) at Visits 3, 4 and 5 and will also provide two cervical tissue biopsy samples at a single time point, Visit 5. These participants will be asked to opt-in to the intensive PK subset.

A total of 96 participants will provide plasma, 45 participants will provide vaginal fluid via tear test strip(s) and 15 will provide cervical tissue.

Detailed instructions are provided in the MTN-024/IPM 031 SSP Manual available at http://www.mtnstopshiv.org.

Table 9: PK Specimen Collection Schedule

Visit	Specimens Collected for PK
Visit 3: 4-Week	• Plasma (n= 96) • Vaginal fluid via tear test strip(s) (n= 45)
Visit 4: 8-Week	• Plasma (n= 96) • Vaginal fluid via tear test strip(s) (n= 45)
Visit 5: 12-Week	• Plasma (n= 96) • Vaginal fluid via tear test strip(s) (n= 45) • Cervical tissue (n=15)

7.8 Behavioral Measures

Behavioral Assessment

All participants will complete a 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, vaginal and sexual

practices, partner types, condom use, and experiences around menopause. 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 subsequent study visits. Measures used previously in other microbicide trials will be employed.

Product Adherence Assessment

Key adherence measures will be captured by Computer-Assisted Self Interview (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) and IPM 027 (http://www.ipmglobal.org/).

Product Preference/Acceptability Assessment

A product acceptability questionnaire will be administered to participants at Enrollment Visit and the monthly CASI (4-Week, 8-Week) and a more thorough acceptability CASI will be administered at the 12-Week Study Visit. Condom acceptability and HIV prevention product preference will also be assessed at the 12-Week Final Clinic 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 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) and to studies of the VR acceptability and preference as a microbicide delivery method or in contraceptive choice studies.[24, 25]

In-depth Interview

A subset of approximately 24 randomized participants across sites will complete an in-depth interview at the 12-Week Final Clinic Visit. The interview will address study VR use and acceptability during the trial. These interviews 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 in-depth interview. These interviews may be conducted over the computer. The audio from the interview will be recorded and transcribed for analysis.

Data on acceptability and factors affecting adherence will be collected during the in-depth interview. The interviews will include topics such as:

- Challenges to use of study products, specifically in relation to the postmenopausal time
- Effect of VR use on sex
- Perceived benefits and barriers to VR use
- Perceived method(s) preferences for HIV prevention

7.9 Clinical Evaluations and Procedures

Physical exams will include the following assessments:

- General appearance
- Weight
- Vital signs
    - Temperature
    - Pulse
    - Blood pressure
    - Respirations
- Abdomen
- Height (at screening only)
- Lymph nodes*
- Neck*
- Heart*
- Lungs*
- Extremities*
- Skin*
- Neurological*

*may be omitted after the Enrollment Visit

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

The required sequence of procedures and specimen collection performed during pelvic exams will be specified in the MTN-024/IPM 031 SSP Manual.

7.10 Laboratory Evaluations

<u>Local Laboratory</u>

- Urine
    - Urine hCG
    - Urine NAAT for GC/CT
    - Dipstick UA and/or urine culture

- Blood
    - Serum chemistries (AST, ALT, creatinine)
    - Complete blood count with platelets

- HIV-1 serology
- Plasma archive
- Syphilis serology
- FSH

- Pelvic
  - Vaginal pH
  - Rapid Trichomonas test
  - Herpes lesion
  - Saline wet mount for BV
  - Pap smear
  - KOH wet mount for candidiasis
  - Vaginal NAAT for GC/CT

Network Laboratory (NL)

- Blood
  - Confirmation HIV-1 serology for seroconversion
  - Standardized HIV-1 resistance tests
  - Plasma for PK (Pharmacology Core)

- Pelvic
  - CVL and swabs for biomarker assessments
  - Cytobrush for flow cytometry
  - Vaginal fluid for PK (Pharmacology Core)
  - Cervical biopsy for PK (Pharmacology Core)
  - Gram stain of vaginal smear
  - Quantitative vaginal culture

IPM Designated Laboratory

- Study Product
  - Used study VR residual drug level assessment

7.11 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical laboratory practice, in accordance with current US Division of AIDS (DAIDS) Laboratory Requirements, MTN-024/IPM 031 Study Specific Procedures Manual (http://www.mtnstopshiv.org), and site standard operating procedures 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. In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

7.12 Specimen Handling

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

7.13 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

Site IoRs are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer (MO), Protocol Safety Physicians, IPM Representative and SCHARP Clinical Affairs Safety Associate will serve as the PSRT. The MTN Statistical Data Management Center (SDMC) prepares routine AE and clinical data reports (blinded to treatment assignment) for review by the PSRT, which meets via conference call approximately once per month or more frequently as needed throughout the period of study implementation to review safety data, discuss product use management, and address any potential safety concerns.

8.2 Clinical Data and Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise. Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC Clinical Affairs staff, the PSRT and study sponsor, IPM. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

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

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

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

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition is applied to all study groups, and is applied beginning at the time of enrollment, i.e., once participant is randomized. The term “investigational product” for this study refers to the dapivirine VR and placebo VR.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience. In cases of potentially life-threatening events, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where a study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be recorded on study

CRFs. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes.

Study site staff will document in source documents and the appropriate AE Log CRF all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the Division of AIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the Division of AIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009)), except that asymptomatic BV and asymptomatic candidiasis will not be reportable AEs. In cases where a genital AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

8.3.2 Serious Adverse Events

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

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life-threatening, or require hospitalization but may jeopardize the participant or require intervention to prevent one of the outcomes listed in the definition above.

8.3.3 Adverse Event Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. Degrees of relatedness will be categorized according to current DAIDS-approved guidelines. Per the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), the relationship categories that will be used for this study are:

- *Related:* There is a reasonable possibility that the AE may be related to the study agent(s)
- *Not Related:* There is not a reasonable possibility that the AE is related to the study agent(s)

8.4 Expedited Adverse Event Reporting Requirements

8.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 (January 2010) of the Manual for Expedited Reporting of Adverse Events to DAIDS, which is available on the Regulatory Support Center (RSC) website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS Expedited Adverse Event (EAE) Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website, http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC, DAIDSRSCSafetyOffice@tech-res.com.

8.4.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 (January 2010) of the DAIDS EAE Manual, will be used for this study. The study agents for which expedited reporting are required are the dapivirine VR and the placebo VR.

8.4.3 Grading Severity of Events

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

8.4.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study begins once the participant is randomized and continues up through the participant's 13-Week Follow-up Phone Assessment/Study Termination.

- 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 Manual for Expedited Reporting of Adverse Events to DAIDS will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.5 Pregnancy and Pregnancy Outcomes

Pregnant women are excluded from this study and the intended study population is postmenopausal women. In the rare event that a participant becomes pregnant at any time during the course of the study, 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, see Section 7.5.2.

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

8.6 Regulatory Requirements

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

8.7 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 temporarily at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. Unless otherwise specified below, the IoR/designee should immediately consult the PSRT for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent

discontinuation of study product. The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs.

9.1 Grading System

AE severity grading is described in Section 8.4.3.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

9.3 General Criteria for Temporary Hold and/or 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:

- The study VR should be held beginning immediately upon recognition of the first reactive HIV test. If via the algorithm in Appendix II the participant is determined to be HIV-uninfected, she may resume product use. The IoR/designee must permanently discontinue the study VR if HIV-1 infection is confirmed. See Section 9.7 for additional details regarding study termination. (permanent discontinuation)
- Allergic reaction to the VR. (permanent discontinuation)
- Pregnancy. (permanent discontinuation) See Section 9.8 for additional details regarding study termination.
- Reported use of PEP for HIV exposure. (permanent discontinuation)
- Reported use of PrEP for HIV prevention. (permanent discontinuation)
- Reported use of topical or systemic hormone replacement therapy requires a consultation with the PSRT regarding the need to temporarily hold study product. If a hold is required, the PSRT must be consulted prior to resuming study product use
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee.
    - The IoR/designee must consult the PSRT on all temporary product holds for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation.
    - If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee must consult the PSRT to resume product use at that time.

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

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

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

In general, for participants who develop a Grade 3 AE not specifically addressed below, judged by the IoR/designee to be related to study product, and the IoR/designee should consult with PSRT and perform the following, unless otherwise directed by the PSRT:

- Temporarily hold the study product.
- Re-evaluate the participant at least weekly for up to 2 weeks.
- Resume study product if improvement to ≤ Grade 2 is documented within 2 weeks.
- Consult PSRT regarding further product management if improvement to severity ≤ Grade 2 cannot be documented within 2 weeks.

If product use is resumed and the same Grade 3 AE deemed related to study product, recurs at any time, the IoR/designee must temporarily hold study product and consult the PSRT for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the study product.

Grade 4
Participants who develop a Grade 4 AE (regardless of relationship to study product), that is not specifically addressed below, should 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 Genital Sexually Transmitted Infection/Reproductive Tract Infection

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

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

A thorough evaluation of genital complaints is expected in the context of this study; however, syndromic management of genital symptoms is acceptable while awaiting laboratory results if such practice is in line with the local standards of care.

Investigators should use first-line oral or parenteral (in the case of syphilis or gonorrhea, for example) medications when at all possible to avoid intravaginal medication use.

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

- 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, temporarily hold study VR use and consult the PSRT; otherwise continue study VR use

Deep epithelial disruption

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

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

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

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

- Temporarily hold study product
- Perform naked eye evaluation
- Re-evaluate in approximately 3-5 days and resume study VR use if resolved
- If unresolved at approximately 3-5 days, re-evaluate within approximately 2-3 days. If resolved at that time may resume use. If unresolved at this second reevaluation, continue temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard

Unexpected genital bleeding

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

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

- Temporarily hold study product
- Evaluate for GC/CT; consider syndromic management, pending results of testing and per clinician discretion
- If GC/CT detected, provide or prescribe treatment
- If GC/CT is not detected, re-evaluate in approximately 3-5 days. If all symptoms and signs are resolved at that time continue study VR use

Genital petechia(e)

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

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 identified as infected with HIV will be managed or referred for management according to the local standard of care. Participants will be offered additional counseling in the clinic, if needed. If a participant has a positive test for HIV-1, study product will be permanently discontinued by the IoR/designee. Because continued study participation would be of no added benefit to participants, all follow-up visits will be discontinued and participants will be considered terminated from the study. Sites will not be responsible for paying for HIV-related care.

The level of care provided at the referral sites will be at a level that meets or exceeds the community standard for HIV-1 care. Written SOPs for referral for HIV-1 care and treatment are in place at each study site. Study site investigators have identified facilities offering psychological and social services and medical care, including antiretroviral therapy (ART), to people infected with HIV-1. Some of the research sites are part of health care institutions that provide HIV-1 care and support, and can refer women to those services. Other sites have established referral agreements with programs to expand access to ART.

Results of study laboratory testing may be helpful in clinical management; these results are provided to the participant and her medical provider as soon as they are available.

9.8 Pregnancy

In the rare event that a participant becomes pregnant during the study, the study product must be permanently discontinued.

A participant who is pregnant at the 12-Week Final Clinic Visit/Early Termination Visit 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 are reported on relevant CRFs; outcomes meeting criteria for EAE reporting also are reported on EAE forms.

A participant who becomes pregnant during the course of the study will have study product permanently discontinued and will be considered terminated from the study per Section 7.5.2.

A participant who becomes pregnant during the course of study participation may be offered participation in MTN-016, the HIV Prevention Agent Pregnancy Exposure Registry, if available at site. This registry study is anticipated to capture pregnancy outcomes as well as infant health information, (including growth and development), to evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy.

For additional details about obtaining pregnancy outcome, please reference the MTN-024/IPM 031 SSP Manual (www.mtnstopshiv.org).

9.9 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The IoR also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if the study sponsor, the MTN, IPM, 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 multi-site, double-blinded, two arm, 3:1 randomized, placebo-controlled trial to assess the safety of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks during 12 weeks of study product use by healthy, sexually active, HIV-uninfected postmenopausal females, as compared with a placebo VR. A total of approximately 96 postmenopausal females (72 in the dapivirine VR arm and 24 in the placebo VR arm) will be randomized.

10.2 Study Endpoints

Primary endpoints

Consistent with the primary study objective to assess the safety of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks during 12 weeks of study product use by healthy, sexually active, HIV-uninfected postmenopausal females, as compared with a placebo, the primary safety endpoints are the proportion of females in each of the two arms with:

- Evidence of Grade 2 or higher genital, genitourinary and reproductive system AEs as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009), Addendum 1, (Female Genital Grading Table for Use in Microbicide Studies) judged to be related to study product

- Evidence of Grade 3 or higher AEs as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009)

Secondary endpoints

Consistent with the secondary study objective to evaluate acceptability of study VR expressed as women's preference for the VR compared to other HIV prevention methods in HIV-uninfected postmenopausal women, the following endpoint will be assessed:

- The proportion of participants who find the study VR to be as acceptable as other HIV prevention methods

Consistent with the secondary study objective to evaluate the adherence to the dapivirine VR versus the placebo VR for 12 weeks of continuous use, the following endpoint will be assessed:

- Adherence measures of daily study product use based on self-report for each participant over the study product use period

Consistent with the secondary study objective to evaluate the systemic and local dapivirine exposure, the following endpoint will be assessed:

- Dapivirine concentrations in plasma, vaginal fluid and cervical tissue

Exploratory Endpoints

Acceptability

- Participant's self-report on multiple components of acceptability via attitudinal questions

Adherence

- Residual amount of dapivirine measured in returned VRs
- Dapivirine concentrations in plasma, vaginal fluid, and cervical tissue

Vaginal Microenvironment

- Changes in pH, microflora and biomarkers

Note: Cervical tissue will be collected on a subset of participants taking part in the Cervical Biopsy/Vaginal Fluid Subsets

10.3 Primary Study Hypothesis

MTN-024/IPM 031 hypothesizes that a dapivirine VR will be as safe and well-tolerated as the placebo VR.

10.4 Sample Size and Power Calculations

10.4.1 Primary Endpoints

The proposed total sample size is approximately N=96 postmenopausal females randomized to 2 arms in a 3:1 ratio giving 72 postmenopausal females in the dapivirine VR arm and 24 postmenopausal females in the placebo VR arm. The sample size is based upon the size of similar Phase 2a studies of vaginal microbicide products and includes a 3:1 ratio of drug to placebo arms to allow for the collection of additional safety endpoints in the drug arm while maintaining blinding between arms.

As a means to characterize the statistical properties of this study Table 10 presents the probability (expressed as a percent) of observing zero, at least one, and two or more safety endpoints among the 72 postmenopausal females in the dapivirine VR arm for various 'true' event rates.

Table 10: Analysis of Safety Event Frequency

Event Rate (%)	P (0 events | n=72) (%)	P (≥1 event | n=72) (%)	P (≥2 events | n=72) (%)
0.5	69.7	30.3	5.1
1.0	48.5	51.5	16.2
3.5	7.7	92.3	72.2
5	2.5	97.5	88.1
10	0.05	99.95	99.5
15	0.0	99.99	99.99

An alternative way of describing the statistical properties of the study design is in terms of the true rate based on the observed data. Table 11 shows the exact 2-sided 95% confidence intervals for the probability of an event based on a particular observed rate. For example, if none of the 72 participants using the dapivirine VR experiences a safety event, the 95% exact 2-sided confidence interval for the true rate of event is (0.0%, 4.99%). If we see 2 events, this changes to (0.34%, 9.68%).

Table 11: Exact Two-sided 95% Confidence Intervals Based on Observing a Particular Rate of Safety Endpoints for Arms of Size 72

Observed event rate (%)	Confidence interval (%)
0.0 (0/72)	(0.0, 4.99)
1.4 (1/72)	(0.04, 7.50)
2.8 (2/72)	(0.34, 9.68)

The primary aim of the study is to compare the safety between the two arms (dapivirine VR arm versus placebo VR arm). Assuming a two-sided Fisher's Exact test with α =.10 and 80% or 90% power, Table 12 provides the difference in the rates of safety events (proportion of females experiencing the safety event of interest) between the dapivirine VR arm and the placebo VR arm that is detectable for a given rate in the placebo VR arm. For example, if the true rate of a given toxicity endpoint in the placebo VR arm is 4.2% (1 out of 24 females experiencing a safety event); the proposed sample size provides 90% power to detect safety endpoint rates greater than 30.2% (26.3% with 80% power).

Table 12: Difference in the Rates of Safety Events

Rate in Placebo Arm (%)	Rate in Drug Arm Detectable with 80% Power (%)	Rate in Drug Arm Detectable with 90% Power (%)
4.2 (1/24)	26.3	30.2
8.3 (2/24)	33.0	37.4
20.8 (5/24)	49.5	54.5
41.7 (10/24)	70.6	75.7
62.5 (15/24)	87.8	91.3

10.4.2 Secondary Endpoints

Acceptability Endpoint
To evaluate acceptability, the proportion of participants who at their 12-Week Final Clinic Visit report via acceptability questionnaire that they prefer the ring at least as much as other HIV prevention methods. A sample size of 72 females receiving the dapivirine VR will provide an absolute precision of 10.5% (i.e., half the width of the 95% confidence interval) assuming an observed acceptability of 75%.

Adherence Endpoint
Adherence will be measured by the percentage of women who keep the VR inserted at all times in the vagina over the course of 12 weeks. A sample size of 96 women will provide an absolute precision of 9.1% (i.e., half the width of the 95% confidence interval) assuming an observed adherence of 75%.

Pharmacokinetic Endpoints
The PK endpoint is a description of the end of period (28 day post ring insertion) plasma, vaginal fluid, and cervical tissue dapivirine concentrations at week 4, 8, and 12 which will be compared to the same results in a recently studied population of pre-menopausal adult women (MTN-013). The 28 day assessment in each ring period – just before ring removal –represents near steady-state concentrations in prior dapivirine ring studies. The intent is to determine if the plasma and vaginal fluid dapivirine concentrations are different in postmenopausal women than in pre-menopausal adult women after placement of dapivirine vaginal rings. The vaginal fluid will be collected by tear strip and the cervical tissue will be collected by biopsy in only a subset of women, 45 for tear strip and 15 for biopsy. This more intensively sampled subset was selected to provide a richer dataset of sampling from the female genital tract and chosen to balance feasible logistical complexity which demands a simpler, more sparse sampling approach with the low likelihood of an important difference between postmenopausal and pre-menopausal adult populations.

Approximately 45 women will provide vaginal fluid. The CV% ranges from 118% to 153% depending on time, location, and formulation. Also, there is no evidence of dose-proportionality for the increase from 0.001% dapivirine gel to 0.005% gel, there is no increase (due to either no difference or insufficient power to detect the difference). If one assumes a CV% of 130%, and comparison of MTN-013 (N=12) to MTN-024 (N=22), then with 5% type I error and 80% power, we can exclude a difference as large as 1.04 SD units or a 135% difference.

Approximately 15 women will provide cervical tissue. There are insufficient data published to estimate CV%, but it appears to be quite large. Nel[26] reports a range of tissue dapivirine concentration from 1-43, 1-190, and 1-356 for 0.001, 0.005, and 0.02% dapivirine gel, respectively. If this had the same variation as tenofovir in tissue, the CV% would be 210-240%. So, if one were to assume tenofovir tissue variability and compare MTN-024 (assuming N=11 due to 3:1 randomization) to MTN-013 (N=12 in each arm), then with 5% type I error and 80% power, we can exclude a difference as large as 1.23

SD units or a 275% difference. The sample size estimates are not different whether one assumes equal or unequal variance.

10.5 Participant Accrual, Follow-up and Retention

Based on previous studies of vaginal products, the accrual of 96 eligible participants will take approximately 12 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 3:1 ratio to the two arms of the study. Study arm randomization will be stratified by site to ensure balanced assignment for products at each site. The randomization scheme will be generated and maintained by the MTN SDMC.

10.7 Blinding

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

There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. As described in Section 7.5.4, in the event that an investigator is concerned that a participant might be put at an increased risk by continuing product use, the Investigator may discontinue study product use by this participant; however, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator will notify the PSRT to review and approve the request.

10.8 Data and Safety Monitoring and Analysis

10.8.1 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).

10.8.2 Primary Analysis

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Within-treatment group assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). When use of formal testing to assess differences between users of the placebo VR and users of the dapivirine 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 of the two arms will be compared for baseline characteristics including demographics and laboratory measurements using descriptive statistics.

Safety Endpoints
All females randomized into the study will be included in the primary analysis according to principle of Intent-to-Treat. 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 two arms.

10.8.3 Secondary Analyses

Acceptability
To assess product preference of the study product, the number and percentage of participants who report that they prefer the ring at least as much as other HIV prevention methods (e.g., condom) will be calculated by arm.

Adherence
The average rate of VR use will be calculated in both arms along with 95% confidence intervals. These rates will be based on participant's self-report of product use at 4, 8, and 12 weeks. The difference between adherence rates with its corresponding 95%

confidence interval will be used to assess adherence of the study product compared to placebo.

Pharmacokinetics
A population mean and standard deviation of the end-of-period dapivirine concentrations for each woman will be calculated based on the samples obtained as described above. The population mean from this study will be compared to the population mean and standard deviation from similar end of period dapivirine results for each matrix – plasma, vaginal fluid, and cervical tissue – in MTN-013.

10.8.4 Missing Data

In any situation with missing data, an 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

CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents. Data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with current DAIDS policies.
(http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Default.aspx)

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations regarding testing investigational products, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval for the study 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. (http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/qmppolicy.pdf)

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by Pharmaceutical Product Development, Inc. (PPD) (Wilmington, NC) in accordance with current DAIDS policies. 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, procedures, and documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including US CFR Title 45 Part 46 and Title 21 Parts 50, 56, and 312
- Perform source document verification to ensure the accuracy and completeness of study data
- Verify proper collection and storage of biological specimens
- Verify proper storage, dispensing, and accountability of investigational study products
- Assess implementation and documentation of internal site quality management procedures

The IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the MTN Coordinating and Operations Center (CORE), SDMC, NL, 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 efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR/designee will have obtained IRB approval and the protocol will have been submitted to the FDA. The IoR/designee will permit audits by the NIH, IPM, the FDA, OHRP, MTN CORE, IRBs, 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 informed consent forms, and study-related documents (such as participant education and recruitment materials) are reviewed by an IRB responsible for oversight of research conducted at the study sites. Any amendments to the protocol must be approved by the responsible IRBs prior to implementation.

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

13.2 Protocol Registration

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

Site-specific informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. 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 also be guided by a common study-specific procedures manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN CORE, SDMC, NL and other designated members of the Protocol Team.

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The PSRT will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team as well as the SMC.

13.4 Risk Benefit Statement

13.4.1 Risks

<u>General</u>
It is not expected that this trial will expose human subjects to unreasonable risk.

Pelvic examination and procedures may cause mild discomfort, pressure and/or vaginal bleeding or spotting. Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Disclosure of HIV and STI status may cause worry, sadness or depression. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial as well as social isolation. Trained counselors will be available to help participants deal with these feelings.

Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions when discussing sexual behaviors.

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

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

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

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

As with any vaginally retained product, the possibility of toxic shock syndrome, although rare, exists.

Cervical Biopsy Collection

For a subset of participants, cervical biopsies carry the risk of discomfort or pain during the procedure and for a few hours afterwards. Participants may have spotting (bleeding) for one or two days. Participants may also be at increased risk for STIs and HIV acquisition, if exposed. Participants will be instructed to refrain from sexual intercourse for 3 days before and after the collection of the biopsy. If participants engage in sexual intercourse before the biopsy has healed they may experience some temporary discomfort. There is a small risk of infection and heavier bleeding. Participants will be encouraged to call the clinic to report any AE after the collection, especially if heavy bleeding is noted (soaking through a pad or tampon in an hour or less) or if the participant develops any abnormal odor or discharge from the vagina.

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-positive or at "high risk" for HIV infection). For example, participants could be

treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

13.4.2 Benefits

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

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.

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 (http://rsc.tech-res.com/policiesandregulations/). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

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

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

- The unknown safety and unproven efficacy of the study product
- Randomization and the importance of participants in both 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 records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers to identifying information will be stored in a separate, locked file in an area with limited access. 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. Audio files will be transcribed and destroyed as soon as transcription and analyses are completed. A member of the MTN Behavioral Research Working Group (BRWG) or designee is responsible for ensuring that these files have been destroyed. 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 CORE, SDMC, and/or NL
- Study staff
- Site IRBs

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

13.7 Special Populations

13.7.1 Pregnant Females

Females who test positive for pregnancy at the Screening Visit will not be eligible to participate in this study. Should a participant test positive for pregnancy after Enrollment, a permanent discontinuation of product will be implemented and all follow-up visits will cease, per Section 7.5.2. During the informed consent process, participants will be informed that the study VR is not a method of contraception and the effects of the study VR on a developing human fetus are unknown.

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 21 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 informed consent forms 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

13.10.1 HIV Counseling and Testing

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

13.10.2 Care for Participants Identified as HIV-Positive

An individual who has been identified as infected with HIV-1 will be managed or referred for management according to the local standard of care. Should a woman test positive for HIV after 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

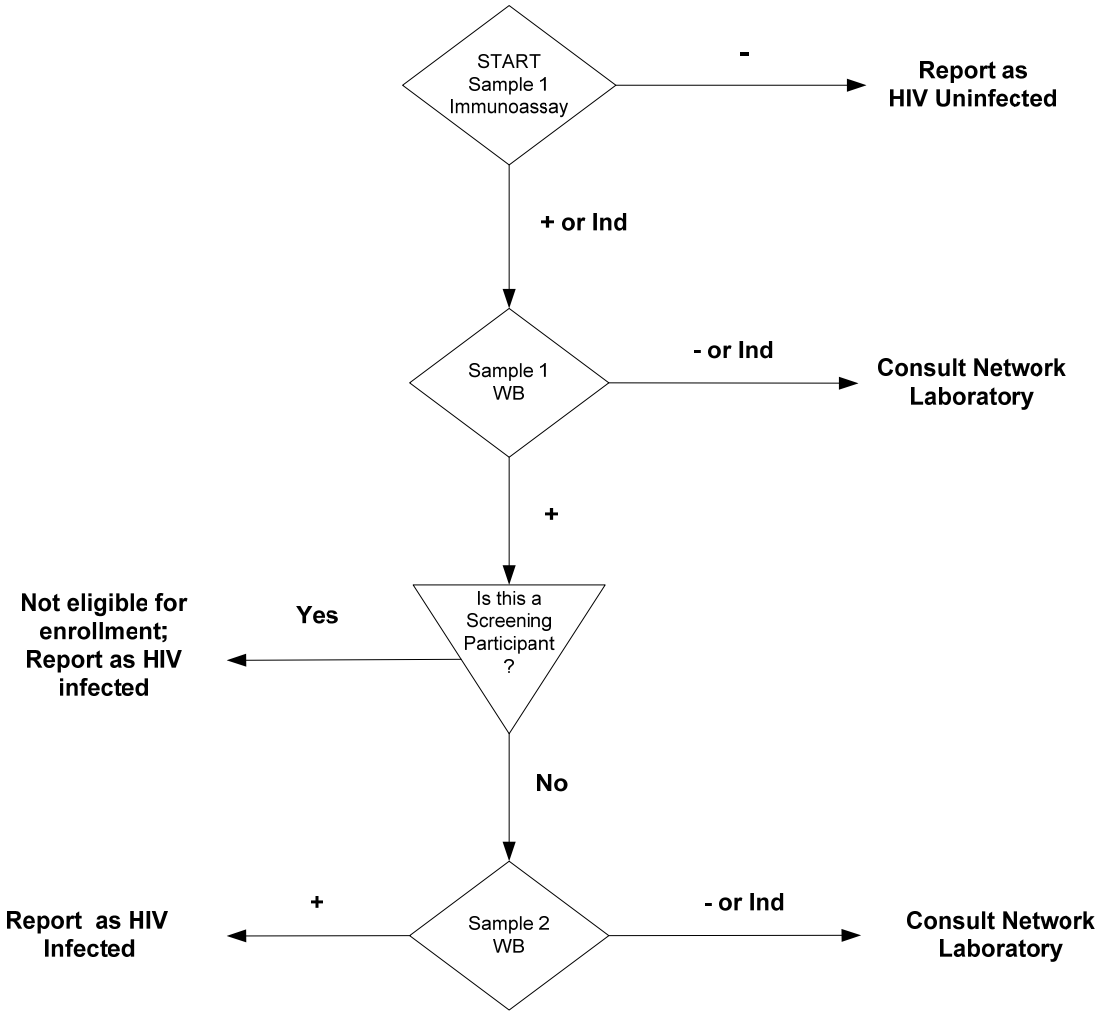
APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCR	ENR	4-Wk Visit	8-Wk Visit	12-Wk Final Clinic Visit/Early Termination Visit	1-Wk and 13- Wk Termination Phone Call
ADMINISTRATIVE AND REGULATORY						
Informed consent(s)	X					
Assign PTID	X					
Locator information	X	X	X	X	X	
Demographic information	X					
Eligibility assessment	X					
Eligibility confirmation		X				
Randomization		X				
Provide reimbursement	X	X	X	X	X	X
Schedule next visit or contact	*	X	X	X	X	
BEHAVIORAL/COUNSELING						
Behavioral assessment		X	X	X	X	
Adherence assessment			X	X	X	
Acceptability assessment		X	X	X	X	
In-depth interview (subset only)					X	
HIV pre and post-test counseling	X	*	*	*	X	
HIV/STI risk reduction	X	X	X	X	X	
Male condom counseling	X	*	*	*	*	
Product adherence counseling		X	X	X		
Protocol adherence counseling		X	X	X		
CLINICAL						
Medical history	X	X	X	X	X	
Menopause Rating Scale		X			X	
Urogenital Distress Inventory (UDI-6 Short Form)		X	X	X	X	
Menstrual history	X					
Concomitant medications	X	X	X	X	X	X
Physical examination	X	X	X	X	X	
Pelvic examination	X	X	X	X	X	
Disclosure of available test results	X	X	X	X	X	
Record/update AEs			X	X	X	X
Treat for UTI/RTI/STIs or refer	*	*	*	*	*	
LABORATORY (vaginal and cervical swabs as required)						
Urine hCG	X	*				
Urine NAAT for GC/CT			*	*	*	
Dipstick UA and/or urine culture, per local standard of care	*	*	*	*	*	
Serum chemistries	X	*	*	*	X	
CBC with platelets	X	*	*	*	X	
HIV-1 serology	X	*	*	*	X	
FSH	X					
PK- Blood			X	X	X	
Syphilis serology	X					
Plasma archive		X				
Gram stain		X	X	X	X	
Vaginal pH		X	X	X	X	
Quantitative vaginal culture		X	X	X	X	
Cytobrush for flow cytometry		Θ			Θ	
CVL for biomarkers		X	X		X	
Vaginal swab(s) for biomarkers		X	X		X	
Vaginal tear test strips for PK (subset only)			X	X	X	
Cervical biopsies for PK (Intensive PK subset only)					X	
Rapid Trichomonas	X	*	*	*	*	
Vaginal NAAT for GC/CT	X	*				

	SCR	ENR	4-Wk Visit	8-Wk Visit	12-Wk Final Clinic Visit/Early Termination Visit	1-Wk and 13- Wk Termination Phone Call
Pap smear interpretation	*					
Saline wet mount for BV	*	*	*	*	*	
KOH wet mount for candidiasis	*	*	*	*	*	
Herpes lesion testing	*	*	*	*	*	
STUDY PRODUCT						
Participants will receive study VR, study product use instructions and will be instructed to self-insert the study VR, followed by bimanual exam to check placement		X	X	X		
Collect study product			X	X	X	
Provision of condoms	*	*	*	*	*	
Provision of lubricant		*	*	*		

X = required, * = if indicated, Θ To be collected on participants with a cervix at selected site(s)

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



Ind: Indeterminate test results

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

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-024/IPM 031
Version 1.0
March 21, 2013

Phase 2a Safety Study of a Vaginal Matrix Ring Containing Dapivirine in a Postmenopausal Female Population

PRINCIPAL INVESTIGATOR: [Sites to insert]
PHONE: [Sites to insert]
SHORT TITLE: Study of Dapivirine Vaginal Ring (VR) in a Postmenopausal Female Population

INFORMED CONSENT
You are being asked to take part in the MTN-024/IPM 031 research study because you are a healthy, HIV uninfected, postmenopausal woman between the ages of 45-65 years old. Approximately 96 women will participate in this study across multiple sites. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). The products being used in this study, dapivirine vaginal ring (VR) and placebo VR are supplied by the International Partnership for Microbicides (IPM). The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to join this study, we want you to know about the study.

This consent form gives you information about the study. The study staff will talk with you about it and answer your questions. Once you read this form, understand the study and if you agree to take part in the study, you will be asked to sign your name on this form. You will be offered a copy of this document to keep. Signing this consent form does not mean you will be enrolled in the study. You must first pass screening tests and exams.

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

PURPOSE OF THE STUDY
The main purpose of this research study is to find out if a VR, containing dapivirine, is safe for postmenopausal women. A VR is a flexible ring placed in the vagina that may or may not contain the study drug. For this study, postmenopausal women are

defined as women who have not had a period in the past 12 months or had their ovaries removed at least 6 months ago.

STUDY PRODUCTS
There are two different vaginal rings that will be used in this study.

The first is a vaginal ring containing dapivirine, a microbicide. A microbicide is a drug or agent being developed to prevent HIV infection. HIV is the virus that causes AIDS. Dapivirine VRs have been tested in women between the ages of 18-45 and were found to be generally safe. Dapivirine works by preventing HIV from making copies of itself, thereby stopping the replication of HIV. This study is not testing to see if dapivirine prevents HIV infection. Researchers do not yet know if dapivirine will work in humans to protect against HIV. Two large studies are being conducted in Africa to understand how well dapivirine works to prevent HIV. Currently, the only known way to prevent HIV is through the consistent use of condoms and through the use of PrEP. PrEP is short for Pre-Exposure Prophylaxis, a new HIV prevention method in which people who do not have HIV take a oral tablet to reduce their risk of becoming infected.

The other vaginal ring in this study is a placebo VR; which does not contain any study drug.

STUDY GROUPS
If you meet all of the study requirements, and you decide to enroll in MTN-024/IPM 031, you will be randomized to one of two VR study groups: dapivirine VR or the placebo VR group. Women will be assigned to a group by random chance (like the rolling dice). More women will receive the dapivirine VR (approximately 72 women) than will receive the placebo VR (approximately 24 women). Both of the study groups are important to this study. You will find out the group you were assigned to at the end of the study, after all participant data has been entered into the database and a final analysis of the primary endpoint(s) has been completed. Women will be asked to insert a new ring once a month for 3 months. It is important that the VR is never worn for longer than 35 days, unless new information is learned that allows you to wear the ring for a longer period of time.

WHAT WILL HAPPEN DURING THE STUDY VISITS?

Visit 1 Screening	Visit 2 Enrollment	Follow-up Phone Call	Visit 3 4- Week Study Visit	Visit 4 8-Week Study Visit	Visit 5 12-Week Final Clinic Visit	Follow-up Phone Call
≤ 45 Days	Day 0	1-Week	4-Week	8-Week	12-Week	13-Week

Table 1: Study visit schedule

Screening Procedures:
MTN-024/IPM 031 has 5 study visits including the Screening Visit which is taking place today, after you sign the informed consent form. The visits will take place here, at this study clinic.

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

- Study staff will ask you where you live and other questions about you, your medical health (including what medications you are taking), menstrual history, your sexual practices and your understanding of the study requirements.
- Study staff will:
  - Perform a physical exam.
  - Talk with you about the requirements of the study including, but not limited to:
    - Not having sex for 72 hours before the study visits
    - Not using study approved lubricant for 72 hours before the study visits
    - Not using hormone replacement therapy or vaginal estrogen creams throughout the duration of your study participation
    - Keeping the vaginal ring in place and not removing it between visits
    - Not using the following for the duration of your study participation: spermicides, female condoms, diaphragms, topical or systemic hormone replacement treatment, including vaginal estrogens, and/or hormonal contraceptives, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), vaginal douches, lubricants not approved for use by this study, moisturizers, sex toys (vibrators, dildos, etc.),
  - Test your urine for pregnancy.
    - If you are pregnant you cannot join this study.
  - Take a blood sample [Sites to insert amount]:
    - To test the health of your blood, liver and kidneys.
    - To confirm that you are postmenopausal, if needed
    - To test for infections passed through sex, including HIV.
      - You will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we are sure of your status. To participate in the study you must have proper 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.
  - Perform a pelvic examination:
    - The study doctor or nurse will use a speculum, a plastic or metal instrument used to separate the walls of the vagina. The study doctor or nurse will check your vagina and cervix for signs of infection, and

other problems. They may also take some fluids to test for sexually transmitted infections or diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary.
    - The study staff may also collect samples from your cervix for a "Pap test" or "Pap smear" if you don't have results from a Pap test done in the past 12 months. 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 have a written report confirming a normal Pap test in the past 12 months or if you had an abnormal Pap test but had follow-up indicating no treatment was required, you will not need to have a Pap test taken at this screening visit. You also will not need a Pap test if you had a hysterectomy for reasons not related to abnormal cells on your cervix. The results of your Pap test may affect whether or not you can continue in the study.
- Give you treatment or refer you for treatment for infections passed through sex, if needed.
- Inform you about other services, if needed.
- Provide you with the results of your tests, if available.
- Schedule your next visit to enroll in MTN-024/IPM 031, if you are willing and eligible.

Results of tests listed above will be available within [*Sites to specify timeframe*] of your visit. If you decide not to join MTN-024/IPM 031, blood collected at this visit will not be kept or used for any tests other than those listed above. The study staff will review your test results with you when they are available. You may return when the results are available.

Enrollment and Follow-up Procedures:

At your Enrollment visit you will:

- Answer questions to confirm you are able to join the study
- Be randomly assigned by study staff to one of two study groups. Neither you nor study staff will know which group you are in, choose your group or change the group you have been placed into. Women in both study groups will have the same study visit schedule.
- Discuss any health or medical problems you may have had.
- Provide a blood sample [insert amount] in case there is a question about your lab results in the future. After all testing is done, this sample will be destroyed.
- Receive and insert the study ring. Study staff may help you insert the study ring if you cannot do it on your own. All participants will have an exam to ensure the ring is inserted correctly.

At <u>most</u> study visits you will:

- Provide and/or update study staff with your contact information (i.e. about where you live and how we can contact you) or update study staff with this information.

- Tell study staff about your health, any changes in your health and/or any other problems since joining the study.
- Talk with study staff about the following:
  - The rules of the study, how to follow the rules, and how to properly wear and use the study ring, including information about how to clean the ring if it falls out (except at your final visit).
  - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex. If you are having sex with a male partner you will also be informed about the benefits of using a condom.
- Have a physical exam.
- Have a pelvic exam.
  - The study doctor or nurse will use a speculum. Study staff will ask if you are experiencing symptoms of an infection. They will check your vagina and cervix for signs of problems due to the ring or infection. They will also take some fluids to test for bacteria and organisms in the vagina and, if necessary, look for any other problems.
  - [Sites participating in the collection of cytobrush for flow cytometry please insert:] At Enrollment and at your final clinic visit you will have cervical fluid collected via cytobrush (if you have a cervix) for research purposes only. You will not be informed of these results as they are collected for research purposes only.
  - At Enrollment, 4-week and at your final clinic visit, a cervicovaginal lavage will be performed. For the lavage a clinician rinses your vagina and cervix (if you have one) with about 2 teaspoons [SITES TO INSERT LOCAL EQUIVALENT] of sterile fluid and collects that fluid in a tube for testing. In addition, a collection of vaginal fluid will be performed via swab(s), like a Q-tip. The cervicovaginal lavage fluid and vaginal fluid collected will be used for research purposes only.
- Receive treatment or be referred for treatment for problems that the study staff may find.
- At all visits, after you begin using the VR, you will have blood collected to see how much of the study product is in your body. The amount of blood collected will not exceed [Sites to insert amount].
- Receive test results, if available.
- Schedule your next visit or phone contact.
- At the Final Clinic Visit, you will provide a sample of blood to:
  - Check the health of your blood, liver and kidneys.
  - Test for HIV.
    - You will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, more tests will be done until your correct HIV status is known. 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.

- You, or the study clinician, will remove the VR in the clinic at weeks 4, 8, 12. Study researchers will keep the rings and may run additional tests on them for research purposes only
- Answer questions about your experience using the VR, including whether or not the ring was removed from or fell out of your vagina, and about any menopausal or bladder symptoms that you may be experiencing. You may use a computer to answer these questions or a staff member may ask you these questions. You may also be selected to be interviewed by study staff at your week 12 clinic visit to talk about your experience using the VR in this clinical trial. This interview may take approximately 45-60 minutes. This conversation will be recorded, but your responses will be kept private and confidential, and the audio-recording will be destroyed after they have been transcribed.
- Answer questions about your use of study-approved products, including lubricant
- Receive male condoms, if you need them.

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

Optional Procedures: Vaginal Fluid and Cervical Tissue Samples

Approximately 45 participants will provide additional samples to help researchers better understand how the study drug enters and exits the body. Approximately 30 participants will provide only vaginal fluid and 15 participants will provide both cervical tissue (2 biopsies) and vaginal fluid.

If you agree to provide extra samples, you will have an exam of your vagina using a speculum. To collect the vaginal fluid, study clinicians will insert a strip of special paper to collect fluid from your vagina. These strips will be collected at weeks 4, 8, and 12, and used to see how much of the study drug is present in your vaginal fluid You do not need to agree to the collection of this fluid to participate in this study.

Another optional procedure is the collection of cervical tissue. Study clinicians will take approximately 2 small tissue samples from your cervix, each about the size of a grain of rice, at week 12. These samples will be used to see how much of the study drug is in your tissue. You do not need to agree to the collection of cervical tissue to participate in this study.

Study staff will talk to you about a few important things to avoid prior to and following the collection of your biopsies. 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. This includes avoiding sexual intercourse, because you may be at higher risk for getting or spreading an infection until the biopsy sites have healed. It is important to

continue using condoms every time you have sex, regardless of how many days it has been since your biopsies were collected. If you insert anything into your vagina in the 3 days prior to the biopsy collection, it is important that you tell a member of the study staff.

Risks of pelvic exam and vaginal fluid collection

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

Risks of Biopsies

You may feel slight to moderate pain at the time of the biopsy (like being pinched) which usually resolves quickly, but could last a few hours. You may have spotting (small amounts of bleeding) for 1 – 2 days. As previously mentioned, you should avoid having sex 3 days before and 3 days after the biopsies; people who are sexually active immediately following a biopsy collection may be at increased risk for STIs and HIV acquisition, if exposed. There is a small risk of the biopsy area becoming infected or having bleeding that is heavier than spotting. It is important for you to know that your body is healing for 24-48 hours after the biopsy is collected. However, if you have heavy bleeding, more than a usual menstrual period, a foul odor or a heavier vaginal discharge (more than usual), you should contact the study clinic right away.

Please initial and date one of the following:

_____ Initials & Date	Yes, if chosen, I agree to provide vaginal fluid only
_____ Initials & Date	Yes, if chosen, I agree to provide both vaginal fluid and cervical tissue
_____ Initials & Date	No, I do not agree to provide vaginal fluid or cervical tissue

If you become infected with HIV

Your participation in this study will not cause HIV infection. However, there is always a chance that through sexual activity or other activities you may become HIV-positive. In the unlikely event that you become HIV-positive, study staff will give you counseling and refer you for medical care and other available services. Your participation in this study will stop. You may be referred to other research studies.

RISKS AND/OR DISCOMFORTS

During pelvic exams, you may feel discomfort or pressure in your vagina and/or pelvis. You may also have vaginal bleeding or spotting. Whenever your blood is drawn, you may have discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection.

Risks of Study Rings

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

- Irritation
- Discharge from the vagina
- Discomfort (including with vaginal intercourse)

Risks of Study Drug

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

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

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.

It is also possible that you may have an allergic reaction to the study product. Signs of an allergic reaction include rash or other skin irritation, itching, joint pain, or difficulty in breathing.

Other Possible Risks

You may become embarrassed and/or worried when discussing your sexual practices, ways to protect against HIV and other infections passed through sex, and your test results. You may be worried while waiting for your test results. If you have HIV or other infections, learning this could cause you to have emotional distress. Finding out your STI or HIV status could also cause problems between you and your

partner. Trained study counselors will help you deal with any feelings or questions you have.

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

Pregnancy

This study is enrolling postmenopausal women, thus the likelihood of women becoming pregnant while participating in this study is extremely unlikely, but we need to tell you about the risks involved if you were to become pregnant.

The VR with active drug and the placebo VR are not birth control methods. We do not know what effect the study drug has on pregnancy, including the effect of the study drug on the fetuses of women who use the VR when pregnant, or the babies of women who use the VR when breastfeeding.

If you become pregnant during the study, study staff will refer you to available medical care and other services you and/or your baby may need. The study does not pay for this care. You will stop using the VR and you will stop coming in for study visits. The outcome of your pregnancy is important to study staff; therefore your pregnancy will be followed until the results of your pregnancy are known.

BENEFITS

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

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

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

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

A description of this clinical trial is 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.

WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT
A study doctor may need to remove you from the study early without your permission if:

- The study is cancelled by the US Food and Drug Administration (FDA), US NIH, the International Partnership for Microbicides (IPM), the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB) (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 (SMC reviews the progress of the study and the kinds of effects participants report)
- You are not able to keep appointments
- Other reasons that may prevent you from completing the study successfully
- You become infected with HIV
- Other administrative reasons

The study doctor may ask you to stop using the study product but continue to come in for follow-up visits and procedures if:

- A study doctor decides that using the VR would be harmful to your safety or well-being, including if you have a bad reaction to the study VR.
- You require a treatment that you may not take while using the study VR.
- You report using post-exposure prophylaxis (PEP) for HIV exposure. PEP refers taking medications to prevent transmission of pathogens after an HIV exposure.
- You report using PrEP for HIV prevention.
- You are unable to comply with the study procedures.

If a study doctor asks you to stop using the VR for one of the reasons mentioned above, you may be asked to come in for all scheduled visits to complete study procedures, but you will stop using the study VR until the study doctor decides it is safe for you to start using it again, if possible.

In the event that you are removed from or choose to leave this study, you will be asked to return your VR. 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. *[Sites to specify allowances for special circumstances.]*

COSTS TO YOU

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

REIMBURSEMENT

[*Sites to insert information about local reimbursement:*] You will receive [*Sites to insert amount* $xx] for your time, effort, and travel to and from the clinic at each scheduled visit. You may receive [Sites to insert amount $xx] for any visits which occur in between your normally scheduled visits. Participants who complete in-depth interviews will receive [Sites to insert amount $xx]. Participants who agree and are selected to provide additional samples will receive [Sites to insert amount $xx] for providing vaginal fluid. Participants who also agree to provide cervical tissue samples will receive [Sites to insert amount $xx].

CONFIDENTIALITY

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

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US OHRP, NIH, and/or contractors of NIH
- IPM, the organization that supplies the study vaginal rings
- Study monitors
- Site IRB
- Study staff

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

The researchers will do everything they can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have

applied for a Certificate of Confidentiality from the US Federal Government. This certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. However, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. This certificate does not prevent you from releasing information about yourself and your participation in the study.

RESEARCH-RELATED INJURY

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

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

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

If you decide not to be in this study, it is possible for you to join other studies, here or at other medical centers/clinics, if studies exist and if you are found to be eligible.

PROBLEMS OR QUESTIONS

If you ever have any questions about the study, or if you have a research-related injury, you should contact *[insert name of the investigator or other study staff]* at *[insert telephone number and/or physical address]*.

If you have questions about your rights as a research participant, you should contact *[insert name or title of person on the IRB or other organization appropriate for the site]* at *[insert physical address and telephone number]*.

Can my private health information and samples collected by this study be stored and used for future studies?

There might be a small amount of your biological specimens (blood, vaginal/ cervical fluids and/or tissue) left over after we have done all of the study-related testing after your study visits. We would like to ask your permission to store these samples and health data related to these samples for use in future studies. If you agree, your samples 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 these samples stored for future studies. If you do not want the samples stored, we will destroy the leftover specimens. Any future studies that may be done will also have to be approved by an IRB. *[Sites to specify institutional policy:]* There is no time limit on how long your samples or health data will be stored or when these leftover specimens may be tested.

_____ Initials & Date	I agree to allow my biological specimens and health data to be used in future research studies.
_____ Initials & Date	I do not agree to allow my biological specimens and health data to be used in future research studies.

SIGNATURES- VOLUNTARY CONSENT

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

Participant Name (print)	Participant Signature	Date and Time
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date and Time
Witness Name (print)	Witness Signature	Date and Time

Reference List

1. UNAIDS, Joint United Nations Programme on HIV/AIDS. UNAIDS Report on the Global AIDS Epidemic 2010. http://www.unaids.org/globalreport/global_report.htm accessed 12 Sept 2012. 2012.
2. CDC Factsheet. HIV/AIDS among persons aged 50 and older, February 2008. http://www.cdc.gov/hiv/topics/over50/resources/factsheets/pdf/over50.pdf accessed 12 September 2012. 2012.
3. Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report, 2007*. Vol. 19. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2009.
4. Prejean J, Song R, Hernandez A et al. Estimated HIV incidence in the United States, 2006-2009. PLoS One 2011;6(8):e17502.
5. Meditz AL, Moreau KL, MaWhinney S, et al. CCR5 Expression Is Elevated on Endocervical CD4+ T Cells in Healthy Postmenopausal Women. JAIDS 2012;59,3:221-228.
6. Fletcher P, Harman S, Azijn H, et al. Inhibition of human immunodeficiency virus type 1 infection by the candidate microbicide dapivirine, a nonnucleoside reverse transcriptase inhibitor. Antimicrob Agents Chemother 2009;53:487-95.
7. Nel AM, Coplan P, van de Wijgert JH, et al. Safety, tolerability, and systemic absorption of dapivirine vaginal microbicide gel in healthy, HIV-negative women. Aids 2009;23:1531-8. 2012.
8. Anderson RM, Swinton J, Garnett GP. Potential impact of low efficacy HIV-1 vaccines in populations with high rates of infection. Proc Biol Sci 1995;261:147-51.
9. IPM. Investigator's Brochure: Dapivirine Vaginal Ring. 30 October 2012.
10. Di Fabio S, Van Roey J, Giannini G, et al. Inhibition of vaginal transmission of HIV-1 in hu-SCID mice by the non-nucleoside reverse transcriptase inhibitor TMC120 in a gel formulation. Aids 2003;17:1597-604.
11. Nel A, Smythe S, Young K, Malcolm K, Rosenberg Z, Romano J. Safety and Pharmacokinetic Assessment of 28 Day Anti-HIV Dapivirine Intravaginal Microbicide Rings In: CROI. Boston; 2008.
12. Nuttall J, Hettema W, van Niekerk N, Nell A. Pharmacokinetics of Monthly Daipiviirine Vaginal Microbicide Rings (Ring-004) for HIV Prevention. In: Microbicides 2012. Syndey; 2012. 2012.
13. Romano J, Variano B, Coplan P, et al. Safety and availability of dapivirine (TMC120) delivered from an intravaginal ring. AIDS Res Hum Retroviruses 2009;25:483-8.
14. Nel A, Kamupira M, Woodsong C, van der Straten A, Monthomery E, van Niekerk N, Nuttall J. Safety, Acceptability and Pharmacokinetic Assessment (Adherence) of Monthly Dapivirine Vaginal Microbicide Rings (Ring-004) for HIV preventionIn: Microbicides 2012. Syndey; 2012.
15. Nel A, Young K, Romano J, Woodsong C, Montgomery E, Masenga G, Rees H, Bekker LG, Ganesh S. Safety & acceptability of silicone elastomer vaginal rings

as potential microbicide delivery method in african women. In: CROI 2011. Boston Feb 27-Mar 2, 2011.
16. Creinin MD, Meyn LA, Borgatta L et al. Multicenter comparison of the contraceptive ring and patch: a randomized controlled trial. Obstet Gynecol 2008;111(2 Pt 1):267-277.
17. Pharmacia & Upjohn Estring® Physician Leaflet. (http://www.pfizer.com/pfizer/download/uspi_estring.pdf). 2013.
18. Warner Chilcott Femring® Full U.S. Prescribing Information. (http://www.warnerchilcott.com/pdfs/pi-femring(physician).pdf).
19. Warner Chilcott Femring® Patient Information Materials: Patient Acceptability. (http://www.warnerchilcott.com/pdfs/pi-femring(patient).pdf).
20. Sormanti M, Shibusawa T. Predictors of condom use and HIV testing among midlife and older women seeking medical services. J Aging Health 2007;19(4):705-719.
21. Zablotsky D, Kennedy M. Risk factors and HIV transmission to midlife and older women: knowledge, options, and the initiation of safer sexual practices. J Acquir Immune Defic Syndr 2003;33 Suppl 2:S122-S130.
22. Lindau ST, Leitsch SA, Lundberg KL, Jerome J. Older women's attitudes, behavior, and communication about sex and HIV: a community-based study. J Womens Health (Larchmt) 2006;15(6):747-753.
23. Sterk CE, Klein H, Elifson KW. Self-esteem and "at risk" women:determinants and relevance to sexual and HIV-related risk behaviors. Women Health 2004;40(4):75-92.
24. Novak A, de la Loge C, Abetz L, van der Meulen EA. The combined contraceptive vaginal ring, NuvaRing: an international study of user acceptability. Contraception 2003;67(3):187-194.
25. Hardy E, Hebling EM, Sousa MH, Almeida AF, Amaral E. Delivery of microbicides to the vagina: difficulties reported with the use of three devices, adherence to use and preferences. Contraception 2007;76(2):126-131.
26. Nel A, Coplan P, Smythe S, McCord K, Mitchnick M, Kaptur P, Romano J. Pharmacokinetic Assessment of Dapivirine Vaginal Microbicide Gel in Healthy, HIV-Negative Women. AIDS Research and Human Retroviruses 2010; 26(11).