MTN-023/IPM 030

Phase 2a Safety Study of a Vaginal Ring Containing Dapivirine in Adolescent Females

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

ACASI	Audio Computer-Assisted Self Interviewing
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
AST	aspartate aminotransferase
AUC	area under the curve
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
BV	bacterial vaginosis
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
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAPY	di-amino-pyrimidine
DLV	delavirdine
DMPA	depot-medroxyprogesterone acetate
DNA	deoxyribonucleic acid
EAE	expedited adverse event
EC	ethics committee
EC_{50}	50% effective concentration
EFV	efavirenz
ENR	Enrollment
FDA	(US) Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
g	grams
GC	*Neisseria gonorrhoeae,* gonorrhea
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
hCG	human chorionic gonadotropin
HEC	hydroxyethylcellulose
HEENT	Head, Eye, Ear, Nose and Throat
HIV	human immunodeficiency virus
hu-PBL	human peripheral blood lymphocytes
IATA	International Air Transport Association
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration

ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IND	Investigational New Drug
IPM	International Partnership for Microbicides
IoR	Investigator of Record
IUD	intrauterine device
KOH	potassium hydroxide
kg	kilogram
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantification
µg	microgram
µM	micromolar
mg	milligram
mL	milliliter
mM	millimolar
MPID	Maternal and Pediatric Infections Diseases Branch
MTN	Microbicide Trials Network
ng	nanogram
nM	nanomolar
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
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no-observed-adverse-effect-level
NRTI	nucleoside reverse transcriptase inhibitor
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
SMS	short message service
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-023/IPM 030

INVESTIGATOR SIGNATURE FORM

Phase 2a Safety Study of a Vaginal Ring Containing Dapivirine in Adolescent Females
Version 2.0
January 14, 2015

A Study of the Microbicide Trials Network

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

IND Holder:
International Partnership for Microbicides (IPM)

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, 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-023/IPM 030

Phase 2a Safety Study of a Vaginal Ring Containing Dapivirine in Adolescent Females

PROTOCOL SUMMARY

Short Title: Study of Dapivirine Vaginal Ring (VR) in Adolescents

Clinical Phase: Phase 2a

IND Sponsor: IPM

Protocol Chair: Kathleen E. Squires, MD

Protocol Co-Chair: Katherine Bunge, MD

Sample Size: Approximately 96 participants

Study Population: Healthy, HIV-uninfected, sexually experienced, adolescent females, 15 - 17 years old (inclusive)

Study Sites: Sites selected by ATN and the MTN Executive Committee

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

Study Duration: Accrual is expected to be completed in approximately 12 months per site. Each enrolled participant will be followed for approximately 25 weeks

Study Products:

- Dapivirine (25 mg) VR
- Placebo VR

Study Regimen: Participants will be randomized in a 3:1 ratio to receive either a silicone elastomer vaginal ring containing 25 mg of dapivirine or a placebo VR. The ring will be replaced every 4 weeks during the 24 week study product use period

Table 1: Study Regimen

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

Primary Objective:

Safety

- To assess the safety of dapivirine (25 mg) administered via a silicone vaginal ring in HIV-uninfected adolescent females, when inserted once every 4 weeks during 24 weeks of study product use

Primary Endpoints:

Safety

- Grade 2 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 the acceptability of the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a 24 week period

Adherence

- To evaluate adherence to the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a 24 week period

Pharmacokinetics

- To evaluate systemic and local dapivirine exposure

Secondary Endpoints:

- Participant's self-report on multiple components of acceptability via attitudinal questions
- Frequency of VR removals and expulsions
- Dapivirine concentrations in plasma and vaginal fluid

Exploratory Objectives:

Acceptability

- To investigate association between systemic and local drug concentration, ring residual drug levels and acceptability

Adherence

- To investigate the association between systemic and local drug concentration, ring residual drug levels and self-reported adherence measures

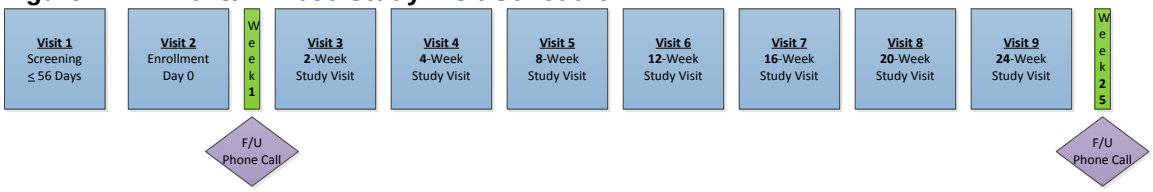
Vaginal Microenvironment

- Describe the genital microenvironment over 24 weeks of study product use

Exploratory Endpoints:

- Participant's self-report on multiple components of acceptability via attitudinal questions
- Frequency of VR removals and expulsions
- Dapivirine concentrations in plasma and vaginal fluid
- Residual amount of dapivirine measured in returned VRs
- Vaginal pH, microflora and biomarkers

Figure 1: MTN-023/IPM 030 Study Visit Schedule



1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Phase 2a Safety Study of a Vaginal Ring Containing Dapivirine in Adolescent Females
Protocol Number:	MTN-023/IPM 030
Short Title:	Study of Dapivirine Vaginal Ring (VR) in Adolescents
Date:	January 14, 2015

1.2 Funding Agencies, IND Sponsor and Monitor Identification

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2 INTRODUCTION

2.1 Microbicides in HIV/AIDS Prevention

According to the Centers for Disease Control & Prevention (CDC), in 2009 individuals aged 13-29 years accounted for 39% of all new HIV infections in the United States.[1] Globally, younger women, aged 15-24 years, are disproportionately affected by the HIV epidemic compared to their male counterparts, as they account for 64% of all HIV infections.[2] In 2013, the United Nations Programme on Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) (UNAIDS) reported that young women of Sub-Saharan Africa were two times more likely to become HIV positive than their male counterparts. Further, adolescents between the ages of 10-19 were the only age group in which AIDS deaths rose between 2001 and 2010.[3]

Factors influencing the risk of HIV among young female populations include a lack of awareness regarding safe sexual practices, cultural and gender incapacity to insist on male partner condom use and modes of HIV transmission, biological development, psychosexual maturation, and sociocultural context; which may mitigate the known benefits of proven HIV prevention methods such as condom use, male circumcision and abstinence.[4]

Safe and efficacious HIV prevention clinical trials have demonstrated proof of concept with Truvada® and tenofovir 1% gel when applied using the BAT 24 dosing regimen.[5] It is predicted that utilization of microbicides that are 60 percent or more efficacious by a small proportion of women in highly HIV prevalent settings could prevent 2.5 million HIV infections over three years.[2] Vaginal rings (VR) may be one strategy to provide discrete and extended protection for females. VRs are flexible and release drug over a prolonged period of time. Studies of VR use for contraception indicate an increase in adherence and satisfaction among adult female users over time, although few contraceptive studies have confirmed or refuted such findings among adolescents.[6]

The International Partnership for Microbicides (IPM) has joined with the Microbicide Trials Network (MTN) to evaluate the safety of dapivirine VR in an adolescent female population. The dapivirine VR is currently being tested in two pivotal Phase 3 efficacy trials enrolling women aged 18-45 years. MTN-023/IPM 030 will contribute valuable adolescent-specific safety data for a potential biomedical HIV-prevention product, dapivirine VR.[7]

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.[8] The dapivirine VR is a flexible ring containing 25 mg of

dapivirine dispersed in a cured silicone matrix. Dapivirine is known to be well-suited for delivery via VR, as evidenced by favorable safety and pharmacokinetic data described below.

Dapivirine was originally developed by Janssen Research and Development (formerly Tibotec Pharmaceuticals) (Titusville, NJ) as an oral antiretroviral (ARV) compound for treatment of HIV/AIDS and was tested in Phase 1 and 2 clinical trials in more than 200 participants.[9] Dapivirine is 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) other than HIV-1. It is, therefore, not intended for use against HIV-2 or other STIs. Dapivirine does not have any contraceptive properties.[10] Detailed information on dapivirine is available in the Dapivirine VR Investigator's Brochure (IB).[11]

The 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 dapivirine from Ring-004 to the cervicovaginal vault over at least 35 days, at which point vaginal fluid concentrations of dapivirine remained at least 3000 times higher than the *in vitro* 99% inhibitory concentration (3.3 ng/mL) in cervical tissue;[11]
- 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 Janssen Research and Development (formerly 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) contains 25 mg of dapivirine. Ring-004 is a dapivirine VR containing 25 mg of dapivirine dispersed in a cured silicone matrix.

2.3 Placebo VR

2.3.1 Description

The placebo VR is a flexible, cured silicone ring, identical to dapivirine Ring-004, containing no active drug. The placebo ring includes approximately 0.02% titanium dioxide colorant to maintain blinded conditions during clinical evaluation.

2.3.2 Mechanism of Action

The placebo VR is 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.[8, 12]

The anti-HIV activity of dapivirine was also confirmed in an *ex vivo* model using human cervical explant cultures. Greater than 99% inhibition was observed at dapivirine concentrations down to 10nM (3.3 ng/mL) and 100nM (32.9 ng/mL) was able to block transfer of free virus by migratory cells to indicator T-cells. In an *in vivo* humanized severe combined immunodeficient (hu-SCID) mouse model, dapivirine gels prevented a systemic infection with either CCR5 or CCR5/CXCR4 virus strains at concentrations of 2,25 µM (0.7 µg/mL) and higher, with efficacy ranging from approximately 70 to 100%, depending on the gel formulation used.[8, 12]

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.[8]

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 was 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.[8]

2.4.2 Condom Compatibility Studies of Dapivirine

Results from male and female condom compatibility studies, IPM 029 and IPM 033, respectively, are available.

Chemical compatibility studies with different dapivirine-containing gel formulations have been conducted on the following types of condoms:[5]

- 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)
- Nitrile condoms with silicone lubricant (female condom)

The results of condom compatibility testing indicate that dapivirine-containing vaginal gel formulations (0.05%) have no deleterious effects on the integrity of male or female condoms, as indicated by tensile condom properties tested pre- and post-treatment. Two clinical condom functionality studies (one with male condoms [IPM 029] and one with female condoms [IPM 033]) were conducted with a placebo vaginal ring (silicone elastomer ring containing no active ingredient). Results from both studies showed that the difference between the total clinical failure rate between condom use with the vaginal ring and condom use without the vaginal ring was less than the pre-defined non-inferiority margins (3% for the male condom study and 8% for the female condom study). Condom use was safe and well tolerated with vaginal ring use.

2.5 Animal Studies of Dapivirine

Pharmacokinetics

Systemic exposure to dapivirine was low following vaginal administration of dapivirine gels to rabbits.[8] 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 were moderate in non-pregnant rats 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, following 14 days of oral administration dapivirine concentrations were highest in the liver and muscle, approximately 9 times higher. Concentrations in the lymph nodes and the brain were about 5 times higher 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.[8]

Toxicology

The toxicity of dapivirine has been evaluated in a comprehensive program of preclinical studies.[11] 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.[11] 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.[11] 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.[11]

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.[12] 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, 27 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted: [5]

- Eight trials of dapivirine VRs (25 mg and 200 mg loads) in which 469 participants were assigned to dapivirine VRs,
- Eight trials of dapivirine vaginal gel in which 491 participants used dapivirine vaginal gel,
- And, eleven trials of oral dapivirine among 211 participants.[2]

Efficacy and safety results from MTN-020 and IPM 027 will be made available to MTN-023 participants if the MTN-023 trial is still ongoing.

Clinical Pharmacokinetics

In all clinical trials of dapivirine vaginal rings and gels to date, dapivirine concentrations in plasma have been very low (less than 2 ng/mL) or undetectable after up to 84 days exposure. Plasma levels of dapivirine after vaginal exposure in clinical trials are 1000-fold lower than maximum plasma concentrations after oral administration of dapivirine (*e.g.* Cmax after 300 mg b.i.d. for 14 days was 2286 ng/mL). [5]

The clinical pharmacokinetic profile of Ring-004 in IPM 013 showed a rapid increase in plasma and vaginal fluid concentrations of dapivirine after ring insertion, resulting in maximum concentrations in plasma by Day 7 and in vaginal fluids between Day 1 and Day 14, after which concentrations decreased steadily over the remainder of a 28-day or 35-day ring use period. Plasma dapivirine concentrations did not exceed 1 ng/mL,

and were therefore well below concentrations at the maximum tolerated dose (MTD) for multiple oral doses (300 mg b.i.d. for 14 days; plasma Cmax of 2286 ng/mL). For dapivirine in vaginal fluids, the highest concentration was observed in the area where the ring was placed, followed by the cervix, with the lowest concentrations near the introitus.

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

Safety

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

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

Trial Details			Number of Participants				
Trial Number	**Description**	**Country**	**Ring-001 reservoir (200 mg)**	**Ring-002 reservoir (25 mg)**	**Ring-003 matrix* (25 mg)**	**Ring-004 matrix** (25 mg)**	**Placebo Ring**
MTN-013/ IPM 026***	Safety and PK in women	United States				12	12
IPM 028	Drug-drug Interaction (miconazole nitrate); 28 days	Belgium				36	0
IPM 034	Safety and PK in women; 7, 14, 28, 56, or 84 days	Belgium				40	0
TOTAL participants			**12**	**18**	**8**	**172**	**195**

*Tin-catalyzed matrix ring.

**Platinum-catalyzed matrix ring

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

Across all clinical trials with multiple ring configurations in healthy participants, the dapivirine VR was safe and well-tolerated.[12] IPM has conducted a review of aggregate safety information which identified vaginal candidiasis as a possible adverse drug reaction associated with dapivirine vaginal ring use. The highest reported severity for vaginal candidiasis across studies was a Grade 2 in women using a Vaginal Ring-004.

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).[15] 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 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 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.

Ring-004, the current formulation, is a dapivirine matrix VR containing 25 mg of drug substance dispersed in a platinum -cured silicone matrix. It has been evaluated in 5 completed clinical trials.[5]

The first clinical trial, IPM 024 was 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. Of the participants using dapivirine VRs, 50% experienced Grade 1 or Grade 2 metrorrhagia, 38% experienced vulvovaginal discomfort and 25% experienced nasopharyngitis. One participant experienced a Grade 1 vaginal hemorrhage in the dapivirine VR group.

IPM 013 was a Phase I, randomized, double-blind, placebo-controlled trial conducted over 3 months at one research center in Belgium (IPM 013).[5] Forty-eight healthy, HIV-negative, sexually active women, 18 to 40 years of age, were assigned in groups of eight to one of two groups, Group A or Group B (unblinded assignment). Within each group, participants were randomized in a blinded manner, in a 3:1 ratio, to either the dapivirine ring or placebo ring, for a total of four treatment arms. In Group A, the first vaginal ring was removed on Day 28, and a second vaginal ring inserted after 3 days, on Day 31, for another 28 days. In Group B, the first vaginal ring was removed on Day 35, and a second vaginal ring was inserted after 3 days, on Day 38, for another 21 days. A third vaginal ring was inserted immediately following removal of the second ring on Day 59, and was worn for 24 hours. No SAEs were reported during the trial. One participant discontinued the trial due to a TEAE of generalized pruritus; the event was not considered serious, of Grade 2 (moderate) intensity, and regarded by the investigator as possibly related to use of the dapivirine ring. No TEAEs were assessed by the investigator as definitely or probably related to the dapivirine ring, and a similar percentage of participants in the dapivirine and placebo ring groups had TEAEs considered to be possibly related to the vaginal ring.

IPM 015 was a double-blind, randomized, placebo-controlled Phase 1/2 trial conducted at 10 research centers in Kenya, Malawi, Tanzania and South Africa. The trial was performed in 280 healthy, HIV-negative women who inserted a vaginal ring once every 21-35 days over a 12-week period. Five SAEs occurred during the trial, of which four occurred in placebo participants.[11] None of the SAEs were judged to be related to product. No TEAEs led to premature discontinuation of ring use. One participant in the dapivirine treatment group reported Grade 3 tonsillitis, which was unrelated to the investigational product. Four participants in the placebo treatment group reported one

instance each of bronchiectasis (Grade 3), peritonsillar abscess (Grade 3), suicide attempt (Grade 3), and hemopneumothorax (Grade 4). The hemopneumothorax was caused by a physical assault; this event was unrelated to the investigational product. A chemical pregnancy was reported for one participant in the placebo ring group who discontinued product use, but continued to attend the research center for safety evaluations and completed the remainder of trial visits. In IPM 015, two vaginal bleeding events were reported; both occurred in the placebo ring arm. Apart from the latter two events, chemical pregnancy and hemopneumothorax, none of the SAEs or TEAEs led to premature discontinuation of ring use.

IPM 028, the fourth trial of Ring-004 was a Phase I open-label, randomized, 3-period, 2-sequence, cross-over trial, to assess the drug-drug-interaction potential between Ring-004 and miconazole nitrate, administered as a single dose (1200 mg) vaginal capsule (Gyno-Daktarin®) in HIV-negative women, 18 to 40 years of age.[5] The trial was conducted at a Phase I unit in Belgium and enrolled 36 women, randomly assigned to one of two treatment sequences, ABC or BAC, during which they received three treatments, each separated by a washout period of 3 weeks: Treatment A = Dapivirine Vaginal Ring-004 inserted for 28 days; Treatment B = Dapivirine Vaginal Ring-004 inserted for 28 days along with a single dose of miconazole nitrate on Day 0; Treatment C = a single dose of miconazole nitrate inserted on Day 0. One SAE (fracture of the right acetabulum) was reported in a participant during the washout period who had been assigned to initial treatment with the dapivirine ring and miconazole vaginal capsule (Treatment B). The event was assessed as severe (Grade 3) and regarded by the Investigator as unrelated to the IP. One TEAE was considered by the Investigator as related to IP use during the trial. The participant was enrolled in Treatment Sequence ABC and experienced moderate (Grade 2) vulvovaginal candidiasis during the ring use period of Treatment A, two days before the scheduled ring removal. Based on all safety evaluations performed, no overall clinically significant differences were observed between treatment with the dapivirine vaginal ring alone, in co-administration with miconazole, or miconazole alone.

IPM 034, the fifth trial of Ring-004 was a Phase I open-label, parallel group trial, to assess the release profile of Ring-004 over extended periods of ring use in HIV-negative women, 18 to 40 years of age. The trial was conducted at a Phase I unit in Belgium and enrolled 40 women in five groups (Groups A, B, C, D and E) of eight women each. Each woman was administered with one dapivirine ring and instructed to wear the ring continuously for a period of 7, 14, 28, 56, or 84 days (1, 2, 4, 8, or 12 weeks). One SAE (thoracic vertebral fractures following a motor vehicle accident) was reported in a participant using the dapivirine ring in Group C. The event was assessed as severe (Grade 3) and regarded by the Investigator as unrelated to the IP. Product-related TEAEs were reported for four women during the trial of whom three experienced mild vaginal discharge (one woman with a 56-day ring use period and two women with an 84-day ring use period) and one experienced moderate bacterial vaginitis (84-day ring use period). Based on all safety evaluations performed during the trial, no overall clinically significant differences were observed between the different ring use periods.

MTN-013/IPM 026, a Phase 1 safety and pharmacokinetics study of dapivirine VR, maraviroc VR, dapivirine/maraviroc VR and placebo VR, enrolled approximately 48 women between the ages of 18-40. The participants were randomized in a 1:1:1:1 ratio to 28 days of continuous study vaginal ring use. Over the course of 52 days, 14 follow-up visits occurred. There was no statistically significant difference in the number of participants with genitourinary AEs between placebo arm and any other treatment arms. Twenty-two women experienced 33 grade 1 and one grade 2 related genitourinary AEs.[12] Two grade 2 AEs were determined to be related to study product. At Day 28, dapivirine vaginal fluid levels were 14.9 µg/mL in women assigned to the dapivirine only ring.

In March of 2012, IPM 027, also known as The Ring Study, was initiated. IPM 027 is a randomized, double-blind, placebo-controlled efficacy and long-term safety study that will enroll 1,650 healthy, HIV-uninfected women, ages 18-45. The study is being conducted in South Africa and Uganda. Study participants will use either the dapivirine ring or the placebo ring every four weeks over approximately two years. The main goals of The Ring Study are to evaluate the long-term safety and efficacy of the dapivirine ring for the prevention of HIV-1 as compared to a placebo ring, when used by healthy, HIV-negative women over a two-year period. Additional goals include measuring the incidence of curable STIs, HIV-2 and pregnancy; monitoring ring acceptability (how well women like using the ring) and adherence (if women use the ring as intended) as reported by the study participants; and tracking the development of any HIV-1 drug resistance in participants who become HIV positive during the study. The study is anticipated to conclude in 2015/16.

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

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%).[16] 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.[16]

2.7.2 Adherence of Dapivirine Vaginal Ring

In IPM 011, 11% of the women experienced ring removal/expulsions, with the most common reason for ring removal/expulsion being 'menses related'. In the majority of cases (64%), the ring was washed and re-inserted.[18]

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 had been removed, the most common reason reported by participants for ring removal was cleaning. The most frequent activity associated with expulsion was urination/defecation. Furthermore, 17-36% (Weeks 2-12) of women reported having sexual intercourse while the ring was out of the vagina.[16]

2.8 Study Hypotheses and Rationale for Study Design

2.8.1 Study Hypotheses

MTN-023/IPM 030 hypothesizes that the dapivirine VR will be safe and well-tolerated for once-monthly use among healthy, adolescent 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 the copolymer evatane, 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". Further, vaginal rings provide an acceptable alternative method for the consistent delivery of contraception for adolescent youth.[19, 20] 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.

Estring® (estradiol vaginal ring) is a VR that is also made from silicone elastomer and contains estradiol 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.[21]

Femring® (estradiol acetate vaginal ring), a cured silicone elastomer 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 flashes) and symptoms of vulvar and vaginal atrophy (e.g., dryness).

Although these rings differ slightly from 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. 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.

Pharmacokinetics

Vaginal fluid and blood for PK will be collected at follow-up visits. Tissue and intensive PK sampling have not been included in this safety study. In the event variations in drug levels between this adolescent population and an adult population are noted, additional studies may be considered.

MTN-023/IPM 030 will fill a void in the dapivirine VR research portfolio, providing the necessary safety data in sexually experienced adolescent females. These data will be added to the efficacy data anticipated from MTN-020 and IPM 027.

3 OBJECTIVES

3.1 Primary Objective

Safety

- To assess the safety of dapivirine (25 mg) administered via a silicone vaginal ring in HIV-uninfected adolescent females, when inserted once every 4 weeks during 24 weeks of study product use

3.2 Secondary Objectives

Acceptability

- To evaluate the acceptability of the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a 24 week period

Adherence

- To evaluate the adherence to the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a 24 week period

Pharmacokinetics

- To evaluate systemic and local dapivirine exposure

3.3 Exploratory Objectives

Acceptability

- To investigate association between systemic and local drug concentration, ring residual drug levels and acceptability

Adherence

- To investigate the association between systemic and local drug concentration, ring residual drug levels and self-reported adherence measures

Vaginal Microenvironment

- Describe the genital microenvironment over 24 weeks of study product use

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-023/IPM 030 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 24 weeks) in sexually experienced, HIV-uninfected adolescent females.

4.2 Summary of Endpoints

Primary Endpoints:

- Grade 2 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:

- Participant's self-report on multiple components of acceptability via attitudinal questions
- Frequency of VR removals and expulsions
- Dapivirine concentrations in plasma and vaginal fluid

Exploratory Endpoints:

- Participant's self-report on multiple components of acceptability via attitudinal questions
- Frequency of VR removals and expulsions
- Dapivirine concentrations in plasma and vaginal fluid
- Residual amount of dapivirine measured in returned VRs
- Vaginal pH, microflora and biomarkers

4.3 Description of Study Population

The study population will be healthy, HIV-uninfected, sexually experienced, adolescent females who meet criteria outlined in Sections 5.2 and 5.3.

4.4 Time to Complete Accrual

Accrual is expected to be complete in approximately 12 months at each site.

4.5 Study Groups

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

- Dapivirine (25 mg) VR
- Placebo VR

4.6 Expected Duration of Participation

The expected trial duration for participants is approximately 25 weeks.

4.7 Sites

Sites selected by ATN and MTN Executive Committee will participate in MTN-023/IPM 030.

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, but not limited to, adolescent and primary care health clinics, family planning clinics, and gynecology clinics, as well as community-based locations. It is anticipated that all participating MTN-023/IPM 030 sites will have established relationships with adolescent clinics, pediatric group practices, children's hospitals, etc. Participants also will be referred to the study from other local research projects and other health and social service providers serving the target study population. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use per local requirements.

> *Note: In case of significant incidental findings, study staff, with written permission from the participant and the participant's parent and/or guardian, may contact the medical care provider to inform him/her of the participant's involvement in MTN-023/IPM 030.*

5.1.2 Retention

Once a participant is enrolled/randomized in MTN-023/IPM 030, 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 are responsible for developing and implementing local site standard operating procedures (SOPs) to achieve the targeted retention rate. Components of such procedures may include the following:

- Thorough explanation of the study visit schedule and procedural requirements during the informed assent/parental permission process, and re-emphasis at each study visit. Also, as part of the informed consent process, encouragement of participants to discuss potential study participation with their partners and other influential family members.
- Thorough explanation of the importance of both study groups to the overall success of the study.
- Collection of detailed locator/contact information at the study screening visits, and active review and updating of this information at each subsequent visit.
- Use of adolescent-appropriate approaches to visit reminders, such as technology-based reminders will be sent by study staff,
- Immediate and multifaceted follow-up on missed visits

Study sites may use a participant tracking database to facilitate visit scheduling and timely identification and follow-up on missed visits. The protocol team, as well as the MTN Study Monitoring Committee (SMC), track retention rates closely and work with study sites as needed to take any required action to address below-target retention rates.

5.2 Inclusion Criteria

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

1) Age 15 through 17 years (inclusive) at Enrollment, verified per site SOPs

2) Able and willing to provide written informed assent/consent and able to obtain written parental or guardian permission (as specified in site SOP) to be screened for and to enroll in MTN-023/IPM 030

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

4) Able to communicate in spoken and written English

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

6) Per participant report at Screening and Enrollment, willing to abstain from inserting anything into the vagina for 72 hours prior to each follow-up visit, including abstaining from penile-vaginal intercourse

   Note: In the event the vaginal ring has been expelled and requires reinsertion, repositioning the vaginal ring is permitted

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

8) Assessment of onset and progression of puberty, as measured by Tanner stage 4 or 5 at Screening, per participant report and/or clinician assessment

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

10) Per participant report at Screening, history of sexual intercourse (at least one episode in participant's lifetime)

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

12) Negative pregnancy test at Screening and Enrollment

13) Per participant report, using an effective method of contraception for at least 30 days (inclusive) prior to Enrollment, and intending to continue use of an effective method for the duration of study participation; effective methods include:
    - hormonal methods (except contraceptive ring)
    - intrauterine device (IUD)
    - sterilization (of participant, as defined in site SOPs)

14) At Screening and Enrollment, participant states a willingness to refrain from inserting the following vaginal products and/or objects into the vagina; spermicides, diaphragms, contraceptive vaginal rings, menstrual cups, cervical caps (or any other vaginal barrier method), douches, lubricants, for the 5 days prior to Enrollment throughout the duration of study participation.

    Note: Neither the use of tampons or sex toys, nor participant engagement in coitus is restricted.

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, unless approved by the PSRT

5.3 Exclusion Criteria

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

1) Per participant report at Screening, intends to do any of the following during the study participation period:
    a) become pregnant
    b) relocate away from the study site
    c) travel away from the study site for more than 4 consecutive weeks

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

   Note: Otherwise eligible participants diagnosed with UTI/RTI during Screening will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 56 days of obtaining informed consent for Screening, the participant may be enrolled.

3) Diagnosed with pelvic inflammatory disease and/or an sexually transmitted infection (STI) requiring treatment per current Centers for Disease Control and Prevention (CDC) guidelines within 60 days of Enrollment (inclusive)

4) At Enrollment, has a clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff)**

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

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

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

   a) Known adverse reaction to any of the study products (ever)
   b) Known HIV-infected partner
   c) Non-therapeutic injection drug use in the 12 months prior to Screening
   d) The use of HIV Post-exposure prophylaxis (PEP) and/or Pre-exposure prophylaxis (PrEP) within the 6 months prior to Enrollment
   e) Currently breastfeeding
   f) Last pregnancy outcome within 90 days or less of Screening
   g) Participation in any other research study involving drugs, medical devices, vaginal products, or vaccines, within 60 days of Screening
   h) Participant report of 3 or more penile-vaginal sexual partners in the month prior to Screening
   i) At Enrollment, as determined by the IoR/designee, has any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease

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

Note: Otherwise eligible participants with an exclusionary test may be re-tested during the screening process. Please see the MTN-023/IPM 030 SSP for additional details.

7) Has any other condition that, in the opinion of the IoR/designee, would preclude informed assent/consent, make study participation unsafe, complicate 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 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-023/IPM 030 unless approved by the PSRT. Participation in the following types of studies may be allowed at the discretion of the IoR/designee:

- Participants may take part in ancillary studies if approved by MTN-023/IPM 030 PSRT
- 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-023/IPM 030, 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 a VR containing either 25 mg dapivirine or a placebo VR in a 3:1 ratio. 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 the clinician/designee will insert, 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 as needed at subsequent visits. The attempt of these procedures must be documented at Enrollment. Additional details on handling the VR (ring insertion, removal, procedures in the event of expulsion or loss, including cleaning procedures) will be provided in the MTN-023/IPM 030 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 contains 25 mg of dapivirine. The dapivirine VR must be stored at 68°-77°F with allowable excursion between 59°- 86°F.

6.3.2 Placebo VR

The placebo VR is manufactured with the same components as the drug-containing rings, except that it contains titanium dioxide as colorant, and no active pharmaceutical ingredient. The purpose of the colorant is for maintaining blinded conditions. The placebo VR must be stored at 68°- 77°F with allowable excursion between 59°- 86°F.

6.4 Supply and Accountability

6.4.1 Supply

IPM (Silver Spring, MD) will oversee the manufacture and testing of all study VRs and analyze/release 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 takes place on the day of Enrollment and at monthly follow-up visits until the final clinic visit. Dispensing may also take place at interim (unscheduled) visits, as needed.

6.4.3 Accountability

Each CRS Pharmacist of Record (PoR) is required to maintain complete records of all study products received. The procedures to be followed are provided in the MTN-023/IPM 030 Pharmacy Study Product Procedures Manual.

Each vaginal ring given 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

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 greater than 7 days	Within 7 working days
End of Study	Within 2 working days

If a 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 as soon as possible.

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 the timeframe stated in the table above, the MTN-023/IPM 030 PSRT must be informed.

The VR must be worn for approximately 28 consecutive days at a time and it is recommended not more than 35 days pass before the ring is replaced. If prolonged use of the study VR has occurred, attempts must be made to contact the participant and retrieve the study product.

For each participant, all VRs remaining in the participant's possession must be retrieved at the 24-Week (Final Clinic) Visit. If the participant does not bring her study product to this visit, study staff must arrange to retrieve the VR within 2 business days. If the VR(s) are not retrieved within that timeframe, the MTN-023/IPM 030 PSRT must be informed.

6.5 Study Product Use Counseling

Participants will receive study product use instructions at the Enrollment Visit and at additional follow-up visits, as needed. Written instructions will also be offered at the Enrollment Visit and follow-up visits, as needed. Site staff will counsel participants on VR product use; these will include instructions to refrain from removing the ring (except as directed), instructions for re-insertion in case of accidental ring expulsion, and the necessity of condom use, as the study product has not been proven to prevent STIs, etc. Additional details will be provided in the MTN-023/IPM 030 SSP Manual. Participants will also be counseled on the use of intravaginal medications/products and practices as described in Section 6.7.

6.6 Concomitant Medications

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

Concomitant medications that either inhibit or induce CYP450 enzymes will be permitted. Following the use of dapivirine rings, systemic exposure observed in women

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.

PrEP, PEP and non-therapeutic injection drug use are not permissible and will result in permanent study product discontinuation, see Section 9.3.

6.7 Use of Intravaginal Medications/Products and Practices

All participants will be counseled to avoid the use of non-study vaginal products during the period of their study participation. Concomitant use of the following vaginal products or other devices are prohibited for the 5 days prior to Enrollment throughout the duration of study participation: spermicides, diaphragms, contraceptive vaginal rings, menstrual cups, cervical caps (or any other vaginal barrier method), douches, and lubricants. Participants who report use of these products during study product use periods will be counseled regarding the use of alternative methods. These products will be recorded on forms designed for that purpose and study staff should reference Section 9.3 for temporary hold and/or permanent discontinuation guidelines. Oral or parenteral medications are preferred, when at all possible, to avoid the use of vaginal medications. Please note, neither the use of tampons or sex toys, nor participant engagement in coitus is restricted, however, participants will be instructed to abstain from these practices and from inserting any non-study vaginal products for 72 hours prior to each monthly follow-up visit, including abstaining from penile-vaginal intercourse. Participant report of sexual intercourse in the past 72 hours will be assessed at each follow-up visit where samples are to be collected for PK. Visits need not be rescheduled in the event that a participant reports inserting anything into the vagina in the 72 hours preceding the study visit, see the MTN-023/IPM 030 SSP Manual available at www.mtnstopshiv.org.

Condoms will be provided to study staff for distribution to participants.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is provided in Appendix I. Presented below are additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites are provided in the MTN-023/IPM 030 Study Specific Procedures (SSP) Manual available at www.mtnstopshiv.org.

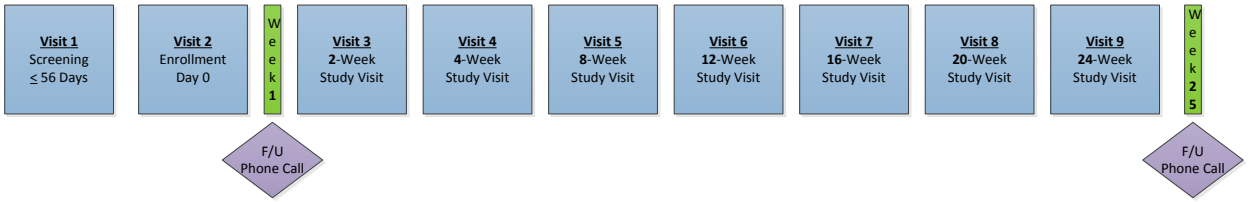


Figure 2: Study Visit Schedule

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 assent/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 56 days prior to the Enrollment Visit. Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed participant assent and parental/guardian permission for screening 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.

Any participant who expresses an interest in involving her current sexual partner in discussions about study participation will be encouraged to bring her partner to the clinic site where a staff member can explain the study and answer any questions the partner may have.

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

Table 4: Screening Visit

Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed assent and parental or guardian consent for Screening and Enrollment and Long-Term Storage of Specimens • Assign participant identification (PTID) • Collect locator information • Collect demographic information • Assess eligibility • Provide reimbursement • Schedule next visit*
Behavioral/Counseling		• Provide counseling ○ HIV pre-and post-test ○ HIV/STI risk reduction ○ Male condom
Clinical		• Obtain medical history • Obtain menstrual history • Obtain concomitant medications • Perform full physical examination • Tanner assessment • Perform pelvic examination • Provide contraceptive counseling • Disclosure of available test results • Treat for UTI/RTI/STI or refer*
Laboratory	**Urine**	• Collect urine for: ○ human chorionic gonadotropin (hCG) ○ Nucleic acid amplification test (NAAT) for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (GC/CT), at sites with capacity ○ Dipstick UA and/or urine culture, per local standard of care*
	Blood	• Collect blood for: ○ Serum chemistries ○ Complete blood count (CBC) with platelets ○ HIV-1 serology (confirmatory tests as needed) ○ Syphilis serology (confirmatory tests as needed)
	Pelvic Samples	• Collect pelvic samples: ○ Vaginal swab for rapid Trichomonas test, at sites with capacity ○ Vaginal swab for Trichomonas/GC/CT♦ ○ Saline wet mount for BV* ○ KOH wet mount for candidiasis* ○ Vaginal pH* ○ Herpes lesion testing*
Study Product Supply		• Provide study condoms*

* If indicated/needed, ♦ At sites using Aptima only

7.3 Visit 2: Enrollment Visit (Day 0)

Enrollment Visit procedures are to be conducted at a single visit.

Table 5: Enrollment Visit

Enrollment Visit		
Component		**Procedures**
Administrative and Regulatory		• Confirm eligibility • Review/update locator information • Randomization • Provide reimbursement • Schedule next visit and/or contact*

Behavioral/Counseling		• Administer baseline behavioral assessment
		• Provide counseling
		  ○ HIV/STI risk reduction
		  ○ Protocol adherence
		  ○ Product adherence
		  ○ HIV pre and post-test
		  ○ Male condom*

Clinical		• Review/update medical history • Review/update menstrual history • Review/update concomitant medications • Perform full physical examination • Perform pelvic examination ○ Including an assessment of cervical ectopy • Provide contraceptive counseling • Disclosure of available test results • Treat for UTIs/RTIs/STIs or refer*

Laboratory	**Urine**	• Collect urine for:
		  ○ hCG
		  ○ NAAT for GC/CT, at sites with capacity*
		  ○ Dipstick UA and/or urine culture, per local standard of care*

	Blood	• Collect blood for:
		  ○ Plasma archive
		  ○ HIV-1 serology (confirmatory tests as needed)
		  ○ Serum chemistries*
		  ○ CBC with platelets*
		  ○ Syphilis serology (confirmatory tests as needed)*

	Pelvic Samples	• Collect pelvic samples:
		  ○ Vaginal swab for Gram stain
		  ○ Vaginal swab for quantitative vaginal culture
		  ○ Vaginal swab for biomarkers
		  ○ Vaginal pH
		  ○ Cervicovaginal Lavage (CVL) for biomarkers
		  ○ Saline wet mount for BV*
		  ○ KOH wet mount for candidiasis*
		  ○ Vaginal swab for rapid Trichomonas test, at sites with capacity*
		  ○ Vaginal swab for Trichomonas/GC/CT*♦
		  ○ Herpes lesion testing*

Study Product Supply		• Participants will receive study VR, study VR use instructions and will be instructed to self-insert the study VR • Clinician directed digit exam to check vaginal ring placement *Note: If the participant is not able to self-insert the study VR, the clinician/designee may assist*

Enrollment Visit	
Component	**Procedures**
	• Provide male condoms*

* If indicated/needed ♦ At sites using Aptima only

7.4 Follow-up Study Visits and Phone Calls

7.4.1 Visit 3: 2-Week Study Visit

Table 6: 2-Week Study Visit

2-Week Study Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next study visit
Behavioral/Counseling		• Provide counseling o HIV/STI risk reduction o Protocol adherence o Product adherence* o HIV pre-and post-test* o Male condom*
Clinical		• Review/update medical history • Review/update menstrual history • Review/update concomitant medications • Record/update AEs • Contraceptive counseling • Disclosure of available test results • Perform targeted physical examination* • Perform pelvic examination* • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o hCG o NAAT for GC/CT, at sites with capacity* o Dipstick UA and/or urine culture, per local standard of care*
	Blood	• Collect blood for: o PK o HIV-1 serology* o Serum chemistries* o CBC with platelets* o Syphilis serology (confirmatory tests as needed)*
	Pelvic Samples	• Collect pelvic samples: o Vaginal pH* o Vaginal fluid for PK o Saline wet mount for BV* o KOH wet mount for candidiasis* o Vaginal swab for rapid Trichomonas test, at sites with capacity* o Vaginal swab for Trichomonas/GC/CT*♦ o Herpes lesion testing*
Study Product Supply		• Provision of male condoms* • Collection of used study VR*

* If indicated/needed ♦ At sites using Aptima only

7.4.2 Visit 4: 4-Week Study Visit

Table 7: 4-Week Study Visit

4-Week Study Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next study visit
Behavioral/Counseling		• Administer behavioral assessment(s) - Adherence • Provide counseling o HIV/STI risk reduction o Protocol adherence o Product adherence o HIV pre-and post-test* o Male condom*
Clinical		• Review/update medical history • Review/update menstrual history • Review/update concomitant medications • Perform targeted physical examination • Perform pelvic examination • Record/update AEs • Provide contraceptive counseling • Disclosure of available test results • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o hCG o NAAT for GC/CT, at sites with capacity* o Dipstick UA and/or urine culture, per local standard of care*
	Blood	• Collect blood for: o PK o HIV-1 serology* o Serum chemistries* o CBC with platelets* o Syphilis serology (confirmatory tests as needed)*
	Pelvic Samples	• Collect pelvic samples: o Vaginal swab for Gram stain o Vaginal swab for quantitative vaginal culture o Vaginal swab for biomarkers o Vaginal fluid for PK o Vaginal pH o Saline wet mount for BV* o KOH wet mount for candidiasis* o Vaginal swab for rapid Trichomonas test, at sites with capacity* o Vaginal swab for Trichomonas/GC/CT*♦ o Herpes lesion testing*
Study Product Supply		• Participants will receive study VR, study VR use instructions and will be instructed to self-insert the study VR *Note: If the participant is not able to self-insert the study VR, the clinician/designee may assist* • Clinician directed digit exam to check vaginal ring placement * • Collection of used study VR • Provision of male condoms*

* If indicated/needed ♦ At sites using Aptima only

7.4.3 Visit 5: 8-Week Study Visit

Table 8: 8-Week Study Visit

8-Week Study Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next study visit
Behavioral/Counseling		• Administer behavioral assessment(s) - Adherence • Provide counseling o HIV/STI risk reduction o Protocol adherence o Product adherence o HIV pre-and post-test* o Male condom*
Clinical		• Review/update medical history • Review/update menstrual history • Review/update concomitant medications • Perform targeted physical examination • Perform pelvic examination* • Record/update AEs • Provide contraceptive counseling • Disclosure of available test results • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o hCG o NAAT for GC/CT, at sites with capacity* Dipstick UA and/or urine culture, per local standard of care*
	Blood	• Collect blood for: o HIV-1 serology* o Serum chemistries* o CBC with platelets* o Syphilis serology (confirmatory tests as needed)*
	Pelvic Samples	• Collect pelvic samples o Vaginal pH* o Saline wet mount for BV* o KOH wet mount for candidiasis* o Vaginal swab for rapid Trichomonas test, at sites with capacity* o Vaginal swab for Trichomonas/GC/CT*♦ o Herpes lesion testing*
Study Product Supply		• Participants will receive study VR, study VR use instructions and will be instructed to self-insert the study VR *Note: If the participant is not able to self-insert the study VR, the clinician/designee may assist* • Clinician directed digit exam to check vaginal ring placement* • Collection of used study VR • Provision of male condoms*

* If indicated/needed ♦ At sites using Aptima only

7.4.4 Visit 6: 12-Week Study Visit

Table 10: 12-Week Study Visit

12-Week Study Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next study visit
Behavioral/Counseling		• Administer behavioral assessment(s) – Adherence & Acceptability • Provide counseling o HIV pre-and post-test o HIV/STI risk reduction o Protocol adherence o Product adherence o Male condom*
Clinical		• Review/update medical history • Review/update menstrual history • Review/update concomitant medications • Perform targeted physical examination • Perform pelvic examination • Record/update AEs • Provide contraceptive counseling • Disclosure of available test results • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o hCG o NAAT for GC/CT, at sites with capacity* o Dipstick UA and/or urine culture, per local standard of care*
	Blood	• Collect blood for: o PK o HIV-1 serology (confirmatory tests as needed) o Serum chemistries* o CBC with platelets* o Syphilis serology (confirmatory tests as needed)*
	Pelvic Samples	• Collect pelvic samples o CVL for biomarkers o Vaginal fluid for PK o Vaginal swab for Gram stain o Vaginal swab for quantitative vaginal culture o Vaginal swab for biomarkers o Vaginal pH o Saline wet mount for BV* o KOH wet mount for candidiasis* o Vaginal swab for rapid Trichomonas test, at sites with capacity* o Vaginal swab for Trichomonas/GC/CT*♦ o Herpes lesion testing*
Study Product Supply		• Participants will receive study VR, study VR use instructions and will be instructed to self-insert the study VR • *Note: If the participant is not able to self-insert the study VR, the clinician/designee may assist* • Collection of used study VR • Clinician directed digit exam to check vaginal ring placement* • Provision of male condoms*

*if indicated/needed ♦ At sites using Aptima only

7.4.4 Visit 7 and Visit 8: 16-Week and 20-Week Study Visits

Table 11: 16-Week and 20-Week Study Visits

16-Week and 20-Week Study Visits		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next contact
Behavioral/Counseling		• Administer behavioral assessment(s) - Adherence • Provide counseling o Protocol adherence o Product adherence o HIV/STI risk reduction o HIV pre-and post-test* o Male condom*
Clinical		• Review/update medical history • Review/update menstrual history • Review/update concomitant medications • Perform targeted physical examination • Perform pelvic examination* • Record/update AEs • Disclosure of available test results • Provide contraceptive counseling • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o hCG o NAAT for GC/CT, at sites with capacity* o Dipstick UA and/or urine culture, per local standard of care*
	Blood	• Collect blood for: o HIV-1 serology (confirmatory tests as needed)* o Serum chemistries* o CBC with platelets* o Syphilis serology (confirmatory tests as needed)*
	Pelvic Samples	• Collect pelvic samples o Vaginal pH* o Vaginal swab for rapid Trichomonas test, at sites with capacity* o Vaginal swab for Trichomonas/GC/CT*♦ o Saline wet mount for BV* o KOH wet mount for candidiasis* o Herpes lesion testing*
Study Product Supply		• Participants will receive study VR, study VR use instructions and will be instructed to self-insert the study VR Note: If the participant is not able to self-insert the study VR, the clinician/designee may assist • Clinician directed digit exam to check vaginal ring placement* • Collection of used study VR • Provision of male condoms *

*if indicated/needed ♦ At sites using Aptima only

7.4.5 Visit 9: 24-Week Final Clinic Visit/ Early Termination Visit

Table 9: 24-Week Final Clinic Visit/Early Termination Visit

24-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(s) – Adherence & Acceptability
		• Provide counseling
		  ○ HIV pre-and post-test
		  ○ HIV/STI risk reduction
		  ○ Male condom*
		• Administer In-depth Interview (subset of participants only)

Clinical		• Review/update medical history • Review/update menstrual history • Review/update concomitant medications • Perform targeted physical examination • Perform pelvic examination ○ Including an assessment of cervical ectopy • Record/update AEs • Provide contraceptive counseling • Disclosure of available test results • Treat for UTIs/RTIs/STIs or refer*

Laboratory	**Urine**	• Collect urine for:
		  ○ hCG
		  ○ NAAT for GC/CT, at sites with capacity
		  ○ Dipstick UA and/or urine culture, per local standard of care*

	Blood	• Collect blood for:
		  ○ HIV-1 serology (confirmatory tests as needed)
		  ○ PK
		  ○ Serum chemistries
		  ○ CBC with platelets
		  ○ Syphilis serology (confirmatory tests as needed)*

	Pelvic Samples	• Collect pelvic samples
		  ○ Vaginal fluid for PK
		  ○ Vaginal swab for Gram stain
		  ○ Vaginal swab for quantitative vaginal culture
		  ○ Vaginal swab for biomarkers
		  ○ Vaginal swab for rapid Trichomonas test, at sites with capacity
		  ○ Vaginal swab for Trichomonas/GC/CT♦
		  ○ Vaginal pH
		  ○ CVL for biomarkers
		  ○ Saline wet mount for BV*
		  ○ KOH wet mount for candidiasis*
		  ○ Herpes lesion testing*

Study Product Supply		• Collection of used study VR • Provision of male condoms *

* If indicated/needed ♦ At sites using Aptima only

7.4.6 Follow-Up Phone Calls: 1-Week and 25-Week Study Termination

Study staff will follow-up with participants via phone call one week following the Enrollment Visit and one week following the 24-Week Final Clinic Visit/Early Termination Visit. Study staff will inquire about AEs the participant may have experienced as a result of the study product or procedures performed during the Enrollment Visit or the 24-Week Final Clinic Visit/Early Termination Visit.

Table 10: 1-Week and 25-Week Study Termination Follow-Up Phone Calls*

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

~ Sites to reference SOPs *Visit procedures may be conducted in-person, see SSP for additional details

7.5 Follow-up Procedures for Participants Who Discontinue Study Product

A participant who discontinues study product will be encouraged to remain in the study if they are willing, for safety evaluations according to the study follow-up schedule with the following exceptions described in the sections below. Please note, in the event a participant permanently or temporarily discontinues study product, regardless of reason, behavioral evaluations will be administered according to guidance from the protocol team.

7.5.1 Participants Who Become Infected with HIV-1

Participants who are seropositive for HIV-1 (per Appendix II) will be referred for medical care. Participants who seroconvert while enrolled in MTN-023/IPM 030 will have CD4, HIV RNA and HIV drug resistance testing performed. Study staff, with written permission from the participant and the participant's parent and/or guardian, may contact the medical care provider to inform him/her of the participant's involvement in MTN-023/IPM 030.

Participants will be permanently discontinued from VR use and will be instructed to return the study VR. The participant will be offered the option to continue follow-up visits per her original study schedule until her originally scheduled study exit date. For those who choose to remain in follow-up, protocol-specified procedures will continue except the following:

- Samples for PK*
- HIV-1 serology
- Provision of HIV pre- and post-test counseling
- Provision of study product and associated procedures
- Provision of product adherence counseling
- Pelvic exams, unless required for AE follow-up

*Perform at the first visit where study product is discontinued, but omit at subsequent visits.

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

7.5.2 Participants Who Become Pregnant

Study staff, with written permission from the participant and the participant's parent and/or guardian, may contact the medical care provider to inform him/her of the participant's involvement in MTN-023/IPM 030.

Participants will be permanently discontinued from VR use and will be instructed to return the study VR. The participant will be offered the option to continue follow-up visits per her original study schedule until her originally scheduled study exit date. For those who choose to remain in follow-up, protocol-specified procedures will continue except the following:

- hCG testing*
- Samples for PK*
- Provision of contraceptive counseling
- Provision of study product and associated procedures
- Provision of product adherence counseling
- Pelvic exams, unless required for AE follow-up

*Perform at the first visit where study product is discontinued, but omit at subsequent visits.

Pregnancy outcomes will be reported on relevant CRFs for participants found to be pregnant at the 24-Week Final Clinic Visit/Early Termination Visit.

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.

7.5.3 Participants Who Voluntarily Discontinue Study Product

All protocol-specified study procedures will continue except:

- Samples for PK*
- Provision of study product and associated procedures
- Provision of product adherence counseling
- Pelvic exams, unless required for AE follow-up

*Perform at the first visit where study product is discontinued, but omit 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:

- Samples for PK*
- Provision of study product and associated procedures
- Provision of product adherence counseling
- Pelvic exams, unless required for AE follow-up

*Perform at the first visit where study product is discontinued, but omit 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, visits and procedures will be documented in participants' study records and on CRFs, when applicable.

7.7 Pharmacokinetics

The MTN-023/IPM 030 cohort will be asked to provide plasma and vaginal fluid for PK at the 2-Week, 4-Week, 12-Week, and 24-Week study visits.

Detailed instructions about sample collection and processing are provided in the MTN-023/IPM 030 SSP Manual available at http://www.mtnstopshiv.org.

Table 11: PK Specimen Collection Schedule

Visit	Specimens Collected for PK
Visit 3: 2-Week	☐ Plasma ☐ Vaginal fluid
Visit 4: 4-Week	☐ Plasma ☐ Vaginal fluid
Visit 6: 12-Week	☐ Plasma ☐ Vaginal fluid
Visit 9: 24-Week	☐ Plasma ☐ Vaginal fluid

7.8 Behavioral Evaluations and Counseling

7.8.1 Behavioral Evaluations

The following behaviors will be assessed either via Audio Computer-Assisted Self Interviewing (ACASI) or CRFs:

Adherence

Adherence will be measured at all monthly visits, including the 24-Week Final Clinic Visit/Early Termination Visit, via questions about the duration that the ring was out of the vagina and reasons for expulsion and removal. In addition, participants will receive and reply to weekly text messages during their product use periods about expulsion and removal. Text messaging may also be used as a reminder to adhere to the monthly study visits.

Acceptability

Acceptability will be measured at the Enrollment, 12-Week and 24-Week Visits, via questions about discomfort due to the VR, feeling the VR during daily activity and sex, ease of insertion and removal, partner awareness of VR during sex, and self and partner attitudes towards the VR.

Sexual activity, condom use and intravaginal practices

These behaviors will be measured at all monthly visits, including at the 24-Week Final Clinic Visit/Early Termination Visit.

In-Depth Interviews

Approximately 6 participants per site will be randomized to complete an in-depth qualitative interview that addresses use of study product during the trial. This interview will be conducted by a trained study interviewer and will follow a structured interview guide. Participants will be asked about their experience with the ring, including questions about their home settings that may have affected ring adherence, social/partner networks that may have affected ring adherence, intercourse experience, partner response to ring use, removal timing, vaginal hygiene, condom use behavior, SMS and image-based ACASI for ease of use, privacy, adherence support and feasibility. The interview will take approximately one hour in duration and will be conducted at the 24-Week Final Clinic Visit/Early Termination Visit.

7.8.2 Product Adherence Counseling

Study product adherence counseling will be provided to all study participants by site staff. Counseling will be provided in accordance with standard methods based on participant-centered strategies with discussions focused on describing experiences and identifying factors facilitating the ease/comfort of product use. Participants will also be counseled on the importance of using the product as prescribed by study clinicians. Counselors will help participants address what they can do or what can be done to increase efficacy of product use.

7.9 Clinical Evaluations and Procedures

Physical Exam

- General appearance
- Weight
- Vital signs

    - Temperature
    - Pulse
    - Blood pressure
    - Respirations
- Abdomen
- Head, Eye, Ear, Nose and Throat (HEENT)
- Height*
- Lymph nodes*
- Neck*
- Heart*
- Lungs*
- Extremities*
- Skin*
- Neurological*

*may be omitted when performing the targeted physical exam

Pelvic Exam

- Vulva
- Perianal area
- Speculum exam
    - Vagina
    - Cervix
- Bimanual exam, if clinically indicated
    - Cervix
    - Uterus
    - Adnexae

The required specimen collection and sequence of procedures during pelvic exams will be specified in the MTN-023/IPM 030 SSP Manual.

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.

7.10 Laboratory Evaluations

Local Laboratory

- Urine
    - Urine hCG
    - Urine NAAT for GC/CT, at sites with capacity
    - Dipstick UA and/or urine culture

- Blood
    - Serum chemistries (AST, ALT, creatinine)
    - Complete blood count with platelets (no differential)
    - HIV-1 serology

- Syphilis serology
- Plasma archive

- Pelvic
  - Vaginal pH
  - Rapid Trichomonas test, at sites with capacity
  - Vaginal swab for Trichomonas/GC/CT at sites planning to use the Aptima only
  - Herpes culture, fluorescent antibody, or PCR
  - Saline wet mount for BV
  - KOH wet mount for candidiasis

Laboratory Center (LC)

- Blood
  - Plasma for PK (Pharmacology CORE)
  - Confirmation HIV-1 serology for seroconversion, as needed
  - Standardized HIV-1 resistance tests, as needed

- Pelvic
  - Vaginal fluid for PK (Pharmacology CORE)
  - CVL for biomarker assessments
  - Vaginal fluid via swab for biomarker assessments
  - 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 and the MTN-023/IPM 030 Study Specific Procedures Manual (http://www.mtnstopshiv.org) for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, 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 and Co-Chair, DAIDS and NICHD Medical Officer (MO), Protocol Safety Physician(s), 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 sponsors. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

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

The PSRT will meet via conference call approximately once per month or more frequently as needed 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 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 can request additional reviews 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 Institutional Review Board (IRB) expeditiously.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition is applied to all study groups, and is applied to all groups beginning at the time of Enrollment (randomization). 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 Adverse Events (AEs) are outlined in Version 2.0 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 EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

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

8.4.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agents for which expedited reporting are required are 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), Version 1.0, December 2004 (Clarification dated August 2009) 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 25-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 females are excluded from this study. If participants become pregnant at any time during the course of the study, participants will be offered the option to remain in the study, but off of study product, per 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, DAIDS MO, and NICHD 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 International Conference on Harmonisation (ICH) guidelines for expedited reporting.

8.6 Regulatory Requirements

Information on all reported CRFs 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.

In addition, as per local regulatory directives, any staff member who has a reasonable cause to believe that any child with whom he/she comes in contact has suffered abuse, or that any person with whom the staff member comes in contact has abused a child, may be required to immediately report their concerns to authorities.

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 (e.g., intimate partner violence, discrimination, stigmatization, etc.) 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 must immediately consult the PSRT for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs.

9.1 Grading System

AE severity grading is described in Section 8.4.3.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

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

A participant will be permanently discontinued or a temporary hold may be initiated from VR product use by the IoR/designee for any of the following reasons:

- Acquisition of HIV-1 infection; such participants will not resume product use at any time. The study VR must be held beginning immediately upon recognition of the first reactive rapid HIV test. 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. (Permanent Discontinuation)
- Allergic reaction to the VR (Permanent Discontinuation)
- Pregnancy (Permanent Discontinuation)
- Breastfeeding (Permanent Discontinuation)
- Reported use of PEP for HIV exposure (Permanent Discontinuation)
- Reported use of PrEP for HIV prevention (Permanent Discontinuation)
- Non-therapeutic injection drug use (Permanent Discontinuation)
- Report of an HIV-positive partner (Permanent Discontinuation)
- Participant is unable or unwilling to comply with required study requirements, 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 relationship to study product, may continue product use.

Grade 3

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

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 unless otherwise decided in consultation with the PSRT, the IoR/designee must:

- 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, must have the study product held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT.

9.5 Genital Sexually Transmitted Infection/Reproductive Tract Infection

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

VR use need not be held in the event of an STI/RTI requiring treatment, unless other temporary product hold/permanent discontinuation guidelines 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. It is recommended that treatment includes first-line oral or parenteral (in the case of syphilis or gonorrhea, for example) medications, when at all possible.

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
- Perform naked eye evaluation
- Re-evaluate by speculum examination in approximately 3-5 days
- If condition worsens 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 affected by erythema or edema

- Continue study VR use
- Perform naked eye evaluation
- Re-evaluate in approximately 3-5 days
- If condition worsens, 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 or severe edema

- Temporarily hold study product
- Perform naked eye evaluation
- Re-evaluate in approximately 3-5 days and reinstate study VR use if resolved
- If unresolved at approximately 3-5 days, re-evaluate within approximately 2-3 days. If resolved at that time, study product use may resume. 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 (See SSP for definition)

- Continue study VR use
- 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)

- Treat for cervicitis and temporarily hold study product
- Evaluate for GC/CT;
- Re-evaluate in approximately 3-5 days. If all symptoms and signs are resolved at that time, resume study VR use

Genital petechia(e)

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

Genital ecchymosis

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

9.7 HIV-1 Infection

A participant who has a positive test for HIV-1 must have study product held. If the participant is subsequently determined to be HIV-negative according to the algorithm in Appendix II, study product may be resumed. If HIV-1 infection is confirmed, study product will be permanently discontinued by the IoR/designee. A participant who is confirmed to be HIV-1 positive during the course of the study will have study product discontinued and will be followed, as per Section 7.5.1.

9.8 Pregnancy

All study participants are required to be using an effective method of contraception according to Section 5.2. Study staff will provide contraceptive counseling to enrolled participants throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery. Study staff also will provide participants with condoms and counseling on use of condoms ideally during every sex act during study participation.

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

A participant who is pregnant at the Final Clinic 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 discontinued and will be followed, as per Section 7.5.2.

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

For additional details regarding obtaining pregnancy outcome, please reference the MTN-023/IPM 030 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 sponsors, the MTN LOC, IPM, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume product use (if applicable) and follow-up through their originally scheduled study exit date, pending consultation with the PSRT.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is a multi-site, double-blinded, two arm, 3:1 randomized, placebo-controlled trial to assess the safety of dapivirine (25 mg) administered in a silicone elastomer vaginal ring, when inserted once every 4 weeks during 24 weeks of study product use by healthy, HIV-uninfected, sexually experienced, adolescent females, 15 - 17 years old (inclusive), as compared with a placebo VR. A total of approximately 96 adolescent 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 ring, when inserted once every 4 weeks during 24 weeks of study product use by healthy, HIV-uninfected, sexually experienced, adolescent females, 15 - 17 years old (inclusive), as compared with a placebo, the primary safety endpoints are the proportion of females in each of the two arms with:

- Grade 2 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

Consistent with the secondary study objective to evaluate the acceptability of the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a 24 week period, the following endpoint will be assessed:

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

To evaluate adherence to the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a 24 week period the following endpoints will be assessed:

- Frequency of VR removals and expulsions
- Dapivirine concentrations in plasma and vaginal fluid

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

- Dapivirine concentrations in plasma and vaginal fluid

Exploratory endpoints

- Participant's self-report on multiple components of acceptability via attitudinal questions
- Frequency of VR removals and expulsions
- Dapivirine concentrations in plasma and vaginal fluid
- Residual amount of dapivirine measured in returned VRs
- Vaginal pH, microflora and biomarkers

10.3 Primary Study Hypothesis

MTN-023/IPM 030 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 adolescent females randomized to two arms in a 3:1 ratio giving 72 adolescent females in the dapivirine VR arm and 24

adolescent 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 13 presents the probability (expressed as a percent) of observing zero, at least one, and two or more safety endpoints among the 72 adolescent females in the dapivirine VR arm for various 'true' event rates.

Table 12: 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 14 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 13: Exact Two-sided 95% Confidence Intervals Based on Observing a Particular Rate of Safety Endpoints for Arms of Size 72

Observed event rate, percentage (fraction)	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 $\alpha = .10$ and 80% or 90% power, Table 15 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 14: Difference in the Observed Rates of Safety Events

True Rate in Placebo Arm, percentage (fraction)	Observed Rate in Drug Arm Detectable with 80% Power, percentage (fraction)	Observed Rate in Drug Arm Detectable with 90% Power, percentage (fraction)
4.2 (1/24)	26.3 (19/72)	30.2 (22/72)
8.3 (2/24)	33.0 (24/72)	37.4 (27/72)
20.8 (5/24)	49.5 (36/72)	54.5 (39/72)
41.7 (10/24)	70.6 (51/72)	75.7 (55/72)
62.5 (15/24)	87.8 (63/72)	91.3 (66/72)

A lower retention rate, 75%, is also considered. Assuming non-differential loss to follow-up, the sample size is then N=72 adolescent females with 54 adolescent females randomized to the dapivirine VR arm and 18 adolescent females in the placebo VR arm. Table 16 presents the probability of observing zero, at least one, and two or more safety endpoints among the 54 adolescent females in the dapivirine VR arm for various 'true' event rates.

Table 15: Analysis of Safety Event Frequency

Event Rate (%)	P (0 events | n=54) (%)	P (≥1 event | n=54) (%)	P (≥2 events | n=54) (%)
0.5	76.3	23.7	3.0
1.0	58.1	41.9	10.2
3.5	14.6	85.4	56.8
5	6.3	93.7	75.9
10	0.3	99.7	97.6
15	0.02	99.98	99.8

Table 17 lists the exact 2-sided 95% confidence intervals for the probability of an event based on a particular observed rate with 75% retention. For example, if none of the 54 participants using the dapivirine VR experiences a safety event, the 95% exact 2-sided confidence interval for the true rate of the event is (0.0%, 6.60%). If we observe 2 events, this changes to (0.45%, 12.74%).

Table 16: Exact Two-sided 95% Confidence Intervals Based on Observing a Particular Rate of Safety Endpoints for Arms of Size 54

Observed event rate, percentage (fraction)	Confidence interval (%)
0.0 (0/54)	(0.0, 6.60)
1.9 (1/54)	(0.05, 9.89)
3.7 (2/54)	(0.45, 12.74)

Table 18 provides the difference in the rates of safety events between the dapivirine VR arm and the placebo VR arm that is detectable for a given rate in the placebo VR arm, assuming a two-sided Fisher's exact test with $\alpha = .10$ and 80% or 90% power when retention is equal to 75%. For example, if the true rate of a given toxicity endpoint in the placebo VR arm is 5.6% (1 out of 18 females experiencing a safety event); the sample size N=72 provides 90% power to detect safety endpoint rates greater than 38.9% (33.3% with 80% power).

Table 17: Difference in the Observed Rates of Safety Events for the Retention Rate of 75%

True Rate in Placebo Arm, percentage (fraction)	Observed Rate in Drug Arm Detectable with 80% Power, percentage (fraction)	Observed Rate in Drug Arm Detectable with 90% Power, percentage (fraction)
5.6 (1/18)	33.3 (18/54)	38.9 (21/54)
11.1 (2/18)	42.6 (23/54)	48.1 (26/54)
27.8 (5/18)	63.0 (34/54)	68.5 (37/54)
55.6 (10/18)	87.0 (47/54)	90.7 (49/54)
66.7 (12/18)	94.4 (51/54)	96.3 (52/54)

10.4.2 Secondary Endpoints

Acceptability Endpoint

Acceptability of the study VR (dapivirine or placebo) in sexually experienced, HIV-negative adolescent females for 24 weeks will be determined by participants rating several components of acceptability (e.g., discreetness, likes and dislikes concerning the ring, attitude toward product characteristics, comfort and ease of use, partner reactions, and effect on sex) on a combination of categorical and continuous scales.

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 24 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 Endpoint

The PK endpoint is a description of the end of period (28 day post ring insertion) plasma and vaginal fluid dapivirine concentrations at week 2, 4, 12 and 24, and will be descriptively compared to the same results in a recently studied population of adult women (MTN-013/IPM 026). Plasma and vaginal fluid will also be collected at Week 2. The 28 day assessment in each ring period 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 adolescent females compared to adult females 28 days after insertion of dapivirine vaginal rings. The vaginal fluid will be collected in 96 females.

Approximately 36 women randomized to active ring will provide vaginal fluid swabs that will be weighed. From previous clinical trials with dapivirine Ring-004 (IPM 013 and IPM 024), the inter-participant CV% of vaginal fluid concentrations of dapivirine prior to ring removal on Day 28 ranged from 35% to 85%, depending on sampling location. If one assumes a CV% of 70%, and comparison of MTN-013/IPM 026 (N=12) to MTN-023/IPM 030 (N=36), then with 5% type I error and 80% power, we can exclude a difference as large as 0.95 SD units or a 67% difference.[11] These historical data for comparison are considered known and fixed. Approximately 36 women randomized to active ring will provide vaginal fluid swabs that will be not be weighed, given logistical constraints, however, these swabs will be analyzed for drug concentration without correction for weight. The variability of drug concentration from the unweighed swab cohort will be compared to the variability in the weighed swab cohort.

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 per site. Participants lost to follow-up and/or on temporary hold or permanent product discontinuation will not be replaced. The team will consider a participant "lost to follow-up" for this trial if she has missed two consecutive study visits and is unreachable by clinic staff after at least three contact attempts. 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 25-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 acceptability of the study products, summary statistics will be calculated on each component of acceptability 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 monthly clinic visits. 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 in each 28-day period 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 and vaginal fluid– in MTN-013/IPM 026, IPM 024, and IPM 013.

10.8.4 Missing Data

In any situation with missing data, an appropriate secondary analysis 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 analysis to assess the potential impact of the missing data will also be performed. This analysis 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, as well as 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 for ATN sites will be carried out by Westat (Rockville, MD) and for MTN site(s) monitoring will be carried out by PPD, Inc. (Wilmington, NC). 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 LOC, SDMC, and LC, IPM and its contractors; National Institute of Allergy and Infectious Diseases (NIAID), NICHD, FDA, OHRP and local and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR/designee will have obtained IRB approval and the protocol will have been submitted to the FDA. The IoR/designee will permit audits by the NIH, IPM, the FDA, OHRP, MTN LOC, IRBs, 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 participation education and recruitment materials) are reviewed by an IRB/EC responsible for oversight of research conducted at the study sites. Any amendments to the protocol must be approved by the responsible IRBs/ECs prior to implementation.

Subsequent to the initial review and approval, the responsible IRBs/ECs must review the study at least annually. Each IoR/designee will make safety and progress reports to the IRBs/ECs 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. MTN site(s) 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

ATN Sites
ATN sites will register the MTN-023/IPM 030 protocol according to NICHD registration processes.

MTN Site
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 for cross-referencing with other INDs for the study products. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement (CTA) executed by NIAID, NICHD, and IPM.

Study implementation will be directed by this protocol, which may not be amended without proper regulatory approvals. Study implementation will also be guided by a common 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 LOC, SDMC, LC and other designated members of the Protocol Team.

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

13.4 Risk Benefit Statement

13.4.1 Risks

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

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

Pelvic examination and procedures may cause mild discomfort and/or vaginal bleeding or spotting.

Disclosure of HIV and STI status may cause worry, sadness or depression. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial as well as social isolation. Trained counselors will be available to help participants deal with these feelings. 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 the use of study product.

Participation in clinical research includes the risk of loss of confidentiality.

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 be perceived to be 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. Further, this study only enrolls sexually experienced adolescent females. It is possible that family members of enrolled participants could learn of a participant's sexual history and/or about their current sexual partner. This could cause stress to the participant or to the family of the participant.

Participants may experience discomfort when answering questions of a personal nature, such as questions dealing with vaginal practices and sexual behaviors.

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

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

It is possible that a participant may have an allergic reaction to the study product.

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

that participants and their partners may feel the ring during sexual activity. As with any vaginally retained product, the possibility of toxic shock syndrome, although rare, exists.

13.4.2 Benefits

Participants in this study may experience no direct benefit. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of safe and effective interventions to prevent HIV transmission. Participants also may appreciate the opportunity to contribute to the field of HIV prevention research.

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

13.5 Informed Consent/Assent Process

Written informed assent will be obtained from each study participant and informed consent from a parent and/or legal guardian prior to initiation of procedures performed at the Screening and Enrollment Visits (i.e., adolescent assent and parental/guardian permission). A written informed consent will be obtained from all enrolled participants who turn the age of 18 during the course of this study. Written informed assent and consent also will be obtained for long-term specimen storage and possible future testing, although consent for specimen storage is not required for study participation. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with current DAIDS policies. Participants and their legal guardians will be provided with copies of the informed assent and consent forms, respectively, if they are willing to receive them.

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 need to practice safe sex behaviors
- The randomization to study product (3:1, active to placebo)
- That participants will not be able to determine which study product they are taking
- 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 unknown safety profile of this product administered in this population
- The right to withdraw from the study at any time

13.6 Participant Confidentiality

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

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

MTN and ATN have 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 Screening or Enrollment Visits will not be eligible to participate in this study. Should a participant test positive for pregnancy after Enrollment, a product hold will be implemented but all follow-up visits will be completed and data collected per Section 7.5.2. A urine pregnancy test will be performed on all women at scheduled study visits, and additionally at interim visits as indicated; the IoR/designee will discontinue study product among participants who test positive for pregnancy. During the informed consent process, females will be informed that 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 will provide knowledge about a female adolescent population, including critical safety data. The risk involved in this study represents a minor risk increase over minimal risk, the data yielded from this study will be essential to providing an HIV prevention method that is female controlled to a known sexually experienced population. The solicitation of participants' assent and the permission of their parents or guardians will be sought, pursuant to guidelines set forth by the 45 CFR 46 and will not be coerced or subjected to undue influence. It is recognized that the planned study population are a vulnerable population and will be treated as such.

13.8 Compensation

Pending IRB/EC approval, participants will be compensated for time and effort in this study, and/or be reimbursed for travel to study visits. Site specific reimbursement 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 to participants throughout the duration of their participation.

13.10.2 Care for Participants Identified as HIV-Positive

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

Identified as HIV-Positive While on Study Product
Please refer to Section 9.7 for further details. Should a female test positive for HIV after Enrollment follow-up procedures will be performed as per Section 7.5.1.

13.11 Study Discontinuation

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

14 PUBLICATION POLICY

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

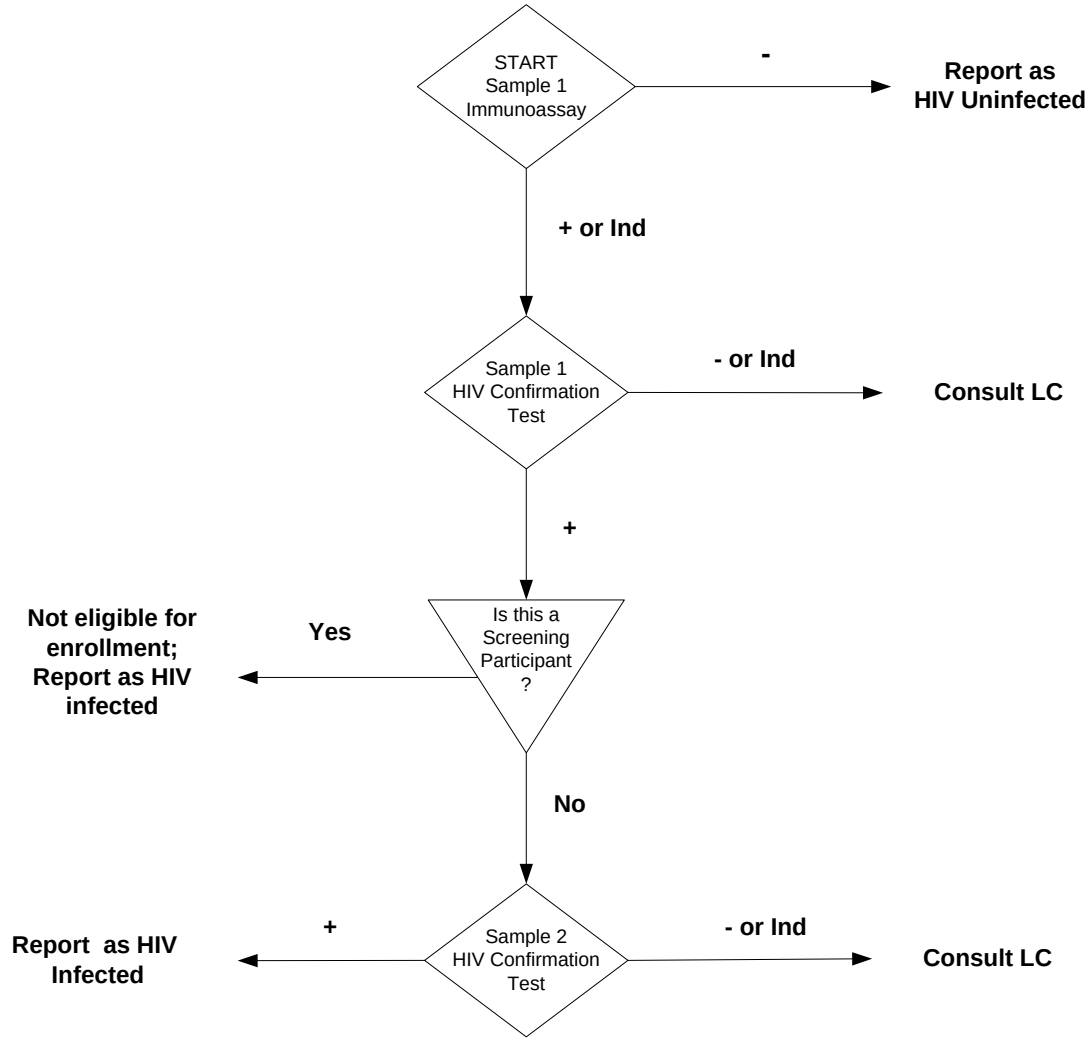
15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCR	ENR	2-Wk Visit	4-Wk Visit	8-Wk Visit	12-Wk Visit	16-Wk Visit	20-Wk Visit	24-Wk Final Clinic Visit/Early Termination Visit	1-Wk Follow-Up and 25- Wk Termination Phone Call+
ADMINISTRATIVE AND REGULATORY										
Informed assent and consent(s)	X									
Assign PTID	X									
Locator information	X	X	X	X	X	X	X	X	X	
Demographic information	X									
Eligibility assessment	X									
Eligibility confirmation		X								
Randomization		X								
Provide reimbursement	X	X	X~	X	X	X	X	X	X	X~
Schedule next visit or contact	*	*	X	X	X	X	X	X	X	
BEHAVIORAL/COUNSELING										
Behavioral evaluation(s)		X		X	X	X	X	X	X	
HIV pre and post-test counseling	X	X	*	*	*	X	*	*	X	
HIV/STI risk reduction counseling	X	X	X	X	X	X	X	X	X	
Male condom counseling	X	*	*	*	*	*	*	*	*	
Protocol adherence counseling		X	X	X	X	X	X	X		
Product adherence counseling		X	*	X	X	X	X	X		
In-Depth Interview									▲	
CLINICAL										
Medical history	X	X	X	X	X	X	X	X	X	
Menstrual history	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Full physical examination	X	X								
Tanner assessment	X									
Targeted physical examination			*	X	X	X	X	X	X	
Pelvic examination	X	X	*	X	*	X	*	*	X	
Assessment of cervical ectopy		X							X	
Disclosure of available test results	X	X	X	X	X	X	X	X	X	
Contraceptive counseling	X	X	X	X	X	X	X	X	X	
Record/update AEs			X	X	X	X	X	X	X	X
Treat for UTI/RTI/STIs or refer	*	*	*	*	*	*	*	*	*	
LABORATORY										
Urine hCG	X	X	X	X	X	X	X	X	X	
Urine NAAT for GC/CT, at sites with capacity	X	*	*	*	*	*	*	*	X	
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	*	*	*	X	*	*	X	
PK- Blood (Plasma)			X	X		X			X	
PK-Vaginal fluid			X	X		X			X	
Syphilis serology	X	*	*	*	*	*	*	*	*	
Plasma archive		X								
Gram stain		X		X		X			X	
Vaginal pH	*	X	*	X	*	X	*	*	X	
Vaginal swab for quantitative vaginal culture		X		X		X			X	
Vaginal swab for biomarkers		X		X		X			X	
CVL for biomarkers		X				X			X	
Vaginal swab for Rapid Trichomonas	X	*	*	*	*	*	*	*	X	
Vaginal swab for Trichomonas/GC/CT	X	*	*	*	*	*	*	*	X	
Saline wet mount for BV	*	*	*	*	*	*	*	*	*	
KOH wet mount for candidiasis	*	*	*	*	*	*	*	*	*	
Herpes lesion testing	*	*	*	*	*	*	*	*	*	
STUDY PRODUCT										
Participants will receive study VR, study VR use instructions and will be instructed to self-insert the study VR		X		X	X	X	X	X		
Clinician directed digit exam to check vaginal ring placement		X		*	*	*	*	*		
Collect study product			*	X	X	X	X	X	X	
Provision of condoms	*	*	*	*	*	*	*	*	*	

X = required, * = if indicated/needed, X~ = sites to reference SOPs, ▲= Subset of participants only, + = Visit procedures may be conducted in-person

APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING FOR SCREENING, ENROLLMENT, AND FOLLOW-UP



Ind: Indeterminate test results
LC: Laboratory Center

APPENDIX III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE)

SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION

MTN-023/IPM 030
Phase 2a Safety Study of a Vaginal Ring Containing Dapivirine in Adolescent Females

DIVISION OF AIDS, NIAID, NICHD, NIMH, NIH

Version 2.0
January 14, 2015

PRINCIPAL INVESTIGATOR: ***[Sites to insert]***
PHONE: ***[Sites to insert]***
Short Title for the Study: Study of Dapivirine Vaginal Ring (VR) in Adolescents

If you are a parent or legal guardian of a child participating on this study, throughout this document "you(r)" = "your child".

INFORMED ASSENT

There will be approximately 96 teenage girls in this study across multiple sites in the United States. 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 and placebo vaginal ring, are supplied by 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 assent form (if you are under the age of 18) gives you information about this study. The study staff will talk with you and your parent/guardian about it and answer your questions, as needed. You may choose to stop being in the study at any time. In order for you to be in the study, both you and your parent/guardian must agree (unless you are an emancipated minor).

Do I have to be in this study?

You do *not* have to be in this study. No one will be angry with you if you decide not to join. You can still get the care you need even if you do not join the study. If you decide to join today you can change your mind later. Once you read, discuss, and understand the study, and if you and your parent/guardian agree, you will be asked to sign your name on this form. You will be offered a copy of this form to keep.

Why is this research being done?

This research study is known as MTN-023/IPM 030. The main purpose of this study is to find out if a vaginal ring containing a drug called dapivirine (study product) is safe and acceptable to teenage girls. Dapivirine works by stopping HIV from making

copies of itself. HIV is the virus that causes AIDS. We do not know whether the study product, dapivirine, can prevent HIV and this study is *not* testing to see if dapivirine prevents you from getting HIV infection. This study is testing to see if the study product released by the vaginal ring is safe and acceptable for teenage girls to use. It is important that you know that vaginal rings containing dapivirine have been tested and found to be generally safe in women between the ages of 18-45.

There are other ongoing research studies to see if the vaginal ring with study product will actually protect females from getting HIV. Two large studies are being conducted in African women to understand how well the study product works to prevent HIV. Currently, the only known way to prevent HIV is through the regular use of condoms and/or through the use of PrEP. PrEP is short for Pre-Exposure Prophylaxis, a new method to prevent HIV infection where people take a medicine to reduce their risk of becoming infected with HIV. Truvada (emtricitabine/tenofovir disoproxil fumarate), a pill that is taken every day is currently the only drug that is approved for PrEP, and only for adults.

The US Food and Drug Administration (FDA) has requested that more studies be done to learn information about what happens when teenage girls use the vaginal ring. This study is being done to see if the vaginal ring with the study product, dapivirine, is safe and acceptable to teenage girls like you.

Who will be in this research study?
Healthy teenage girls who are found to be eligible will be enrolled in the study.

What will I be asked to do if I join this research study?
In this study you will have to wear a vaginal ring for 24 weeks, replacing the vaginal ring every 4 weeks. You will also be asked to come to the clinic for 9 study visits (including the visit today). If you agree to join this study and your parent/guardian provides their permission, you will be in the study for about 25 weeks. Each visit will take approximately [*Sites to insert the approximate length of time*].

You should know that there are two groups in this study. One group will receive a vaginal ring with the study product dapivirine in it. The other group will receive a vaginal ring that looks just like the dapivirine-containing vaginal ring but does not have any study product in it. We call this the placebo vaginal ring. Which vaginal ring you get is decided by chance [*Sites to insert preferred description of 'Randomization'*]. There will be more teenage girls (approximately 72 girls) in the group using the vaginal ring with study product in it than in the group (approximately 24 girls) using the placebo vaginal ring. Neither you nor the staff can decide which group you will be in. Also, neither you nor the staff will know if you are using the vaginal ring with study product or the placebo vaginal ring because both vaginal rings look the same.

What procedures will be performed for research purposes?

Screening Procedures –[*Sites to modify the following section as required by local regulatory authorities to include the specific timing of procedures*]
Your first visit will happen after you read, discuss, understand and sign forms to agree to participate. The procedures done at this visit will take about [*Sites to insert the approximate length of 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, and questions to determine if you are eligible to be in this study
- Study staff will:
  - Perform a physical exam which will include measuring your height, weight, temperature, pulse, blood pressure, and perform other procedures as needed
  - Talk with you about the requirements of the study including, but not limited to:
    - Not having sex for 72 hours before the study visits, if you are currently having sex
    - Not inserting any non-study vaginal products into the vagina for 72 hours prior to each follow-up visit
    - Keeping the vaginal ring in place and not removing it between visits
    - Not using the following for the duration of your study participation and for 5 days prior to enrollment: spermicides, diaphragms, contraceptive vaginal rings, menstrual cups, cervical caps (or any other vaginal barrier method), douches, lubricants not approved for use by this study.
  - Talk with you about birth control and ways to avoid becoming pregnant
    - You will be required to use birth control for at least 30 days before you attend your Enrollment Visit, even if you are not currently having sex. You will be asked to continue to use the same birth control for the duration of your study participation.
  - Test your urine for:
    - Infections
    - Pregnancy
      - If you are pregnant you cannot join this study. If the study is still open after your pregnancy, you can come back here to find out if you are eligible
  - Perform a pelvic examination:
    - The study doctor or nurse will use a speculum to do this exam. A speculum is a plastic or metal tool used to help open the vagina so that the doctor or nurse can examine your vagina and the cervix. They 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 sexually transmitted diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary

- Take a blood sample [*Sites to insert amount*] to test for:
  - Health of your blood, liver and kidneys
  - Infections passed through sex, including HIV
    - You will be told your HIV test result as soon as it is available. You must receive HIV test results to be in the study. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV test results are not clear. In that case, we will do more tests until we know your status for sure. If the test shows that you have HIV, you cannot join the study. However, we will refer you to the medical care and other services that you may need. The study staff will tell you about other studies you may be eligible for, if any.
    - The study staff will talk with you about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex
- Give you male condoms, if you need them
- Give you treatment for urine infections and infections passed through sex, if needed
- Give you referrals for other services, if needed
- Schedule your next visit to enroll in MTN-023/IPM 030, if you are eligible

Results of tests listed above will be available within [*Sites to specify timeframe*] of your visit. The study staff will review your test results when they are available. If the results show you can join the MTN-023/IPM 030 study, the study staff will explain the study again to you and answer any questions you may have.

Enrollment and Follow-up Procedures – [*Sites to modify the following section as required by local regulatory authorities to include the specific timing of procedures*]

If you are found to be eligible, your next visit will be within 56 days of your Screening Visit. The next visit is called the Enrollment Visit. You will receive and begin wearing the vaginal ring at the Enrollment visit. You will have the following study visits and phone calls:

- Enrollment Visit
- 1-Week Follow-up Phone Call
- 2-Week Study Visit
- 4-Week Study Visit
- 8-Week Study Visit
- 12-Week Study Visit
- 16-Week Study Visit
- 20-Week Study Visit
- 24-Week Study Visit
- 25-Week Follow-up Phone Call

Note: The visit schedule may be adjusted if needed.

- You will be asked to avoid inserting the following vaginal products and/or objects into your vagina: spermicides, diaphragms, contraceptive vaginal rings, menstrual cups, cervical caps (or any other vaginal barrier method), douches, or lubricants for the 5 days prior to Enrollment and throughout the duration of study participation.

- You will be asked to receive and reply to phone calls from the study staff. In addition, you will be asked to answer questions about your study product use by text message on a cell phone. You will be reimbursed for each text message session. You will receive text message(s) once a week. Your answer(s) will be private.

- Study staff will:
  - Confirm you are able to join the study and that you understand the study requirements
  - Ask you questions about your vaginal practices
  - Ask you to provide or update information about where you live and how we can contact you
  - Ask you if you have any changes in your health (including what medicines you are taking) and your menstrual periods
  - Describe any health problems or other problems having to do with the study, including the vaginal ring, since your last visit (except at your Enrollment visit)
  - Perform a physical exam at some visits
  - Take a sample of your blood at some visits [Sites to insert amount] to:
    - Test for HIV. You will be told your HIV test result as soon as it is available. You must receive your HIV test results to be in the study. You will talk about the meaning of your results and how you feel about them, and ways to prevent HIV and other STIs. Sometimes HIV test results are not clear. In that case, we will do more tests until we know your results for sure. If the test shows you have HIV, you cannot join the study. We will tell you where you can get care and other services you may need. You will be told about other studies you may be eligible for, if any.
    - Check on the health of your blood, liver and kidneys.
    - To see how much of the study product, dapivirine, is getting absorbed by your body.
  - Test your urine at some visits for:
    - Pregnancy
      - If you are pregnant you cannot join this study. If the study is still open after your pregnancy, you can come back here to find out if you are eligible
    - Infections passed through sex
  - Perfom a pelvic exam at some visits:
    - To check for signs of infection, and other problems.

- To take some fluids from your vagina using a swab for research purposes only. Staff will also take some fluids from your cervix using a swab to test for sexually transmitted infections or sexually transmitted diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary. Some of these swabs may be self-collected. If you are uncomfortable collecting the fluid, a study clinician can collect it for you.
- During some pelvic exams, a vaginal wash will be performed. The study doctor or nurse will rinse your vagina and cervix with about 2 teaspoons [SITES TO INSERT LOCAL EQUIVALENT] of sterile (very clean) fluid, and then will collect the fluid in a tube for testing. The fluid collected will be used for research purposes only.

- Provide the results of your tests, when available
  - You will receive the results of the local laboratory tests (e.g., pregnancy test, liver and kidney function tests, STI tests), but you will not receive results of research laboratory tests (e.g., tests which will tell the researchers how much study product has been absorbed in your body) done specifically for this study. However, we will be monitoring your health while you are on this study and if there are test results that show you should stop taking the study product, or if there are other concerns, you will be informed right away.
- Give you referrals for other services, if needed
- Provide treatment or referral for treatment for problems that the study staff may find.
- Provide counseling. The study staff will discuss:
  - The rules of the study and how to follow the rules (except at your Final Visit)
  - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to prevent HIV and other infections passed through sex
  - Birth control and ways to prevent getting pregnant (except at your Final Visit)

The information you provide during these counseling sessions will not be shared with your parent(s)/guardian(s).

- Give you male condoms, if needed
- Schedule your next visit/contact (except at your Final Visit)

- You will be asked to use a study vaginal ring; as part of using the vaginal ring you will:
  - Talk with study staff about how to properly wear and use the vaginal ring, including information about wearing the vaginal ring during your period, how to clean the vaginal ring if it falls out, etc.
  - Receive and, if you are able, insert a new vaginal ring at each visit. If you are not able to insert the vaginal ring yourself, a study clinician can help you
  - Have an exam to ensure that the vaginal ring is properly inserted, if needed

- Return your vaginal ring to study staff. Study researchers may keep this vaginal ring for additional testing. These tests will help researchers better understand your vaginal ring use.
- In the event that the vaginal ring falls out, you may return to the clinic to have the vaginal ring reinserted if you are uncomfortable doing so yourself. A new vaginal ring will be provided to you, if needed.
- Answer questions about your experience using the vaginal ring, including whether or not the vaginal ring was removed from or fell out of your vagina. You will be asked to answer questions about your vaginal practices. Also you will answer questions about any problems you may have had during your participation in this study.
- You may be asked to answer questions that may make you uncomfortable, for example, questions about drug use or sexual activity. You may use a computer to answer these questions or a staff member may ask you these questions directly. It is important that you know that study staff will ask you these questions in private and your responses will be kept confidential.
- Provide study staff with information regarding your vaginal ring use and other related questions by replying via text message to study staff. You may also be reminded of your study visits via text message.

- At any time during the study, the following may need to be collected if you are having symptoms of infection or if clinicians suspect you may have an infection:
  - Have vaginal and/or cervical swabs collected to test for infections
  - Have a blood sample [Sites to insert amount] collected to test:
    - For infections passed through sex
    - For HIV
    - The health of your blood, liver and kidneys
  - Have urine collected to test for:
    - Pregnancy
    - Infection

It may be necessary for you to make additional visit(s) and/or allow for the collection of additional specimens during your study participation to have any of the study procedures listed above repeated in the event of: abnormal results; difficulties in sample shipping, processing, or testing; and/or if you experience any changes in your physical condition.

In-depth Interview Subset:
About 6 teenage girls from each site will participate in the in-depth interview portion of this study. You may be asked to complete an in-depth interview at the Final Clinic Visit. During this interview, you will be asked to talk about your experience with the vaginal ring, including vaginal ring removal timing, vaginal hygiene, and condom use behavior. Additionally you will be asked about how your vaginal ring use was affected by your home setting, relationships with your friends and/or boyfriend(s) or

girlfriends, and your experience with sex if you are currently sexually active. Questions will be asked regarding the ease of use, privacy, adherence support and feasibility of text messaging and computer survey(s). The in-depth interview will take approximately 60 minutes to complete and will be conducted at the Final Study Visit.

What if I become infected with HIV?

Being in this study will not cause HIV infection. However, there is always a chance that through sex or other activities you could become HIV-positive. If you become HIV-positive, you will stop using the vaginal ring, but you will be asked to continue to come for regularly scheduled visits and for some of the study procedures, if you agree. The study staff will support and refer you for medical care and other available services. If you become infected with HIV, it is possible that you could have dapivirine-resistant HIV, which means that your HIV would still be able to survive in the presence of the study product, dapivirine. A blood test will be performed to find out if you have drug resistance. Results of this test will also help determine which medications would be best to treat your HIV. [*Sites to include/amend the following as appropriate:* If you are interested, study staff will inform you of other research studies you may be eligible for.]

It may be necessary, depending on local and national health requirements, for study staff to report diseases, including HIV, identified among study participants. The reportable diseases at this site are [*Sites to insert*]. We must inform the following [*Sites to insert more detailed information regarding who will be informed of the reportable diseases*].

Pregnancy

The vaginal ring with study product and the placebo ring are not birth control and will not prevent pregnancy. Even if you are not currently sexually active, you must agree to use an effective method of birth control (e.g., birth control pills, hormonal-based methods, intrauterine device (IUD), the patch) but you cannot use a vaginal ring for birth control.

We do not know what effect the study products have on pregnancy, including the effect of the study product on the fetuses of females who use the vaginal ring when pregnant. Because of this, pregnant females may not join this study. Females who join the study must agree to use birth control and have scheduled pregnancy tests while in the study.

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

important to study staff; therefore your pregnancy will be followed until the results of your pregnancy are known.

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws

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

Risks of Genital Exams

You may feel discomfort or pressure during the examination of your genital area and inside your vagina. You may have a small amount of vaginal bleeding which will stop shortly after the exam. During the vaginal wash procedure, you may have a temporary cool feeling in your vagina.

Risks of Study Rings

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

- Discharge from the vagina
- Vaginal irritation and discomfort

As with any product that is placed into the vagina, the possibility of toxic shock syndrome exists, although it is very rare. Toxic shock syndrome is a serious but uncommon infection caused by bacteria. While it is unlikely that you should experience toxic shock syndrome as a result of using the vaginal ring, it is important that you alert the study staff if you experience any of the following symptoms: sudden high fever, a faint feeling, diarrhea, headache, a rash, and muscle aches.

Risks of Study Drugs

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

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

Risks of HIV and Sexually Transmitted Infection (STI) Testing

Being tested for HIV and STIs may cause anxiety regardless of the test results. Receiving a positive test result, indicating that you have an HIV infection or an STI, may have a strong emotional impact. When being tested for HIV infection, there is the possibility that you are in the earliest stage of infection and that the HIV test may not be able to detect the infection

Other Possible Risks

You may become embarrassed and/or worried when discussing sexual activities, if you are currently sexually active, ways to protect against HIV and other infections passed through sex, and your test results. You may be worried while waiting for your test results. If you have HIV or other infections, learning this could make you worried or upset. Finding out your HIV status could also cause problems between you and your partner or your family. Trained study counselors will help you with any feelings or questions you have.

We will make every effort to protect your privacy while you are having the study visits, exams, and tests. Your visits will take place in private. Reports via computer or text messages will be stored in computers that are password-protected and will not include personal information that could identify or link information to you; only your study ID number will be recorded. You will be shown how to erase the text message sessions from your mobile phone by study staff. However, as with all text messages sent from and received on your phone, it is possible that others may see your personal messages. Protections have been made to ensure that questions asked via text message are vague and will not directly convey information about your participation in this research study.

If you are chosen for the in-depth interview subset, study staff will talk with you about how and when you used the study products, and they will audio record the discussion using a digital audio recorder. The audio files will be put into writing by the person interviewing you or by another person who does not know you and does not have your personal information. The audio recordings will be destroyed as soon as they have been put into writing; usually this is about three months after your interview. The person in charge at this site will make sure that these records have been destroyed. You should NOT identify anyone in the in-depth interviews. Also, any names that might be mentioned on the recording will NOT be noted. Instead a generic description will be used in the transcript (i.e., if you refer to a friend's name, "FRIEND1" will be noted).

It is possible that others may learn of your participation in this study, and because of this, may treat you unfairly or discriminate against you. For example, you may feel uncomfortable at school, you could have problems getting or keeping a job, or being accepted by your family, friends, or community. It is also possible for you and/or your partner to feel the vaginal ring during sexual activity, if you are currently sexually active. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

BENEFITS

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

This study cannot provide you with general medical care, but study staff will refer you to another medical provider who can provide you with care.

You will be counseled and tested for HIV and STIs. 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.

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 vaginal ring may be causing bad side effects, you will be told about this. It is important for you to know that other drugs are being tested to prevent getting HIV. Researchers working on this study will provide you with new information about HIV prevention that becomes available, regardless of the product, if it is found to be effective in adolescent females. You will also be told when study results may be available, and how to learn about them.

A description of this clinical trial is available on http://www.ClinicalTrials.gov, as required by the U.S. law. 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 FDA, US NIH, 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)/ the Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of research participants
- The Study Monitoring Committee (SMC) recommends that the study be stopped early. (A SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study)
- You are not able to keep appointments
- Other reasons that may prevent you from completing the study successfully

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

- You become pregnant
- You become infected with HIV
- You are using PrEP for HIV prevention

- You are using PEP due to HIV exposure
- You are using non-therapeutic injectable drugs
- A study doctor decides that using the vaginal ring would be harmful to you
- You require a treatment that you may not take while using the study vaginal ring
- You have a bad reaction to the study vaginal ring

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

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

ALTERNATIVES TO PARTICIPATION
As previously mentioned, currently the only known way to prevent HIV is through the consistent use of condoms and/or through the use of PrEP.

[*Sites to include/amend the following, if applicable:* There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing and birth control. We will tell you about those places if you wish.]

COSTS TO YOU
[Site to complete according to site capacity] There is no cost to you for study related visits, the vaginal ring, physical examinations, laboratory tests or other procedures. Treatments available to you from the study site for infections passed through sex (other than HIV) 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 will receive [*Sites to insert amount* $xx] for responding to text messages. If chosen to take part in the in-depth interview, you will receive [*Sites to insert amount* $xx]. You may receive [Sites to insert amount $xx] for any visits which occur in between your normally scheduled visits.

CONFIDENTIALITY

Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality.

[*Sites to insert details regarding the confidentiality of protected health information and conditions under which the clinician may share protected health information with the participant's parent/guardian*].

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff is required by law to take steps to keep you and others safe. This means that we have to report to the authorities (hospital, police, or social services) any information you tell us that suggests that you might be in danger such as if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you. Also, infectious diseases must be reported to health authorities as required by local law. *[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 *[LOCAL HEALTH AUTHORITY].*

The study staff may use your personal information to verify that you are not in any other research studies. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH
- [*Sites to insert applicable local authorities*]
- IPM, the organization that supplies the vaginal rings
- Study monitors
- Site Institutional Review Board (IRB)/ Ethics Committee (EC), an Ethics Committee is a committee that watches over the safety and rights of research participants
- Study staff

The researchers will do everything they can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. However, if the study staff learns of possible child abuse

and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. This certificate does not prevent you from releasing information about yourself and your participation in the study.

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of study participation. This US federally funded study does not have the ability to provide compensation for research-related injury. If you are injured or become ill from taking part in this study, it is important to tell your study doctor. Emergency treatment may be available but you, your parent/guardian, or your insurance company will be charged for this treatment. You do not give up any legal rights by signing this assent/consent form.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

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

PROBLEMS OR QUESTIONS

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

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

[Sites to omit the following if a separate assent/consent for Storage and Future Testing of Specimens is required]

ASSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION

Please carefully read the statements below and think about your choice. No matter what you decide it will not affect whether you can be in this research study. There might be a small amount of urine, blood, vaginal and cervical fluids left over after we have done all of the study related testing for your study visits. We would like to ask your permission to store your leftover urine, blood, vaginal and cervical fluids, and related health information for use in future studies. If you agree, your samples and related health data will be stored safely and securely. Only approved researchers will have access to the samples. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. There is no time limit on how long your samples will be stored. The specific type of testing planned for these specimens is not yet known, however samples may be used by the MTN Laboratory Center to complete additional quality assurance and control testing, ensuring that the tests perform correctly and supply accurate data. Any future testing, beyond the quality assurance and control testing, will also have to be approved by an Ethics Committee/ Institutional Review Board. No genetic testing (limited or genome-wide) is planned. You can still enroll in this study if you decide not to have urine, blood, vaginal and cervical fluids stored for future studies. You can withdraw your assent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study, and the leftover samples will be destroyed. However, researchers will not be able to destroy samples or information from research that is already underway.

PARTICIPANT INITIALS _____ Initials _____ Date	I DO agree to allow my biological specimens and health data to be stored and used in future research studies.
_____ Initials _____ Date	I DO NOT agree to allow my biological specimens and health data to be stored and used in future research studies.
PARENT/GUARDIAN INITIALS _____ Initials _____ Date	I DO agree to allow my child's biological specimens and health data to be stored and used in future research studies.
_____ Initials _____ Date	I DO NOT agree to allow my child's biological specimens and health data to be stored and used in future research studies.

SIGNATURES- VOLUNTARY ASSENT & PARENT/GUARDIAN PERMISSION

[Insert signature blocks as required by the local IRB/EC:]

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions which I have about my rights as a research participant will be answered by [*INSERT LOCAL IRB INFORMATION*]

ASSENT (For children who <u>are</u> capable of understanding the study procedures and their potential discomforts and benefits).

_____
Minor Participant's Name (Print)

_____ _____
Minor Participant's Signature Date

I understand that, as a minor (age less than 18 years), the above-named adolescent is not allowed to participate in this research study without my permission. I voluntarily agree to allow my daughter to whom I am the legal guardian to be in this research study. A copy of this permission form will be given to me.

_____ _____
Parent's or Guardian's Name (Print) Relationship to Participant (Child)

_____ _____
Parent's or Guardian's Signature Date

VERIFICATION OF EXPLANATION

I certify that I have carefully explained the purpose and nature of this research to (name of participant) in age appropriate language. She has had an opportunity to discuss it with me in detail. I have answered all of the participant's questions and she provided affirmative agreement (i.e., assent) to participate in this research.

_____
Study Staff's Name Conducting
Assent & Parent/Guardian Permission
Discussion (Print)

_____ _____
Study Staff Conducting Date
Assent & Parent/Guardian Permission
Discussion (Signature)

APPENDIX IV: SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE)

SAMPLE INFORMED CONSENT

MTN-023/IPM 030
Phase 2a Safety Study of a Vaginal Ring Containing Dapivirine in Adolescent Females

DIVISION OF AIDS, NIAID, NICHD, NIMH, NIH

Version 2.0
January 14, 2015

PRINCIPAL INVESTIGATOR: ***[Sites to insert]***
PHONE: ***[Sites to insert]***
Short Title for the Study: Study of Dapivirine Vaginal Ring (VR) in Adolescents

INFORMED CONSENT
This consent form (if you reached the age of [*Sites to include the age of majority based on state regulations*] while enrolled in this study or if you are an emancipated minor) gives you information about this study. You may have previously been asked to take part in this research study because you were a female between the ages of 15 and 17 years. There will be approximately 96 teenage girls in this study across multiple sites in the United States. 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 and placebo vaginal ring, are supplied by 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 (or continue in) this study, we want you to know about the study. The study staff will talk with you about it and answer your questions, as needed. You may choose to stop being in the study at any time.

Do I have to be in this study?
You do *not* have to be in this study. No one will be angry with you if you decide not to join. You can still get the care you need even if you do not join the study. If you decide to join today you can change your mind later. Once you read, discuss, and understand the study, and if you agree, you will be asked to sign your name on this form. You will be offered a copy of this form to keep.

Why is this research being done?
This research study is known as MTN-023/IPM 030. The main purpose of this study is to find out if a vaginal ring containing a drug called dapivirine (study product) is safe and acceptable to teenage girls. Dapivirine works by stopping HIV from making copies of itself. HIV is the virus that causes AIDS. We do not know whether the study product, dapivirine, can prevent HIV and this study is *not* testing to see if

dapivirine prevents you from getting HIV infection. This study is testing to see if the study product released by the vaginal ring is safe and acceptable for teenage girls to use. It is important that you know that vaginal rings containing dapivirine have been tested and found to be generally safe in women between the ages of 18-45.

There are other ongoing research studies to see if the vaginal ring with study product will actually protect females from getting HIV. Two large studies are being conducted in African women to understand how well the study product works to prevent HIV. Currently, the only known way to prevent HIV is through the regular use of condoms and/or through the use of PrEP. PrEP is short for Pre-Exposure Prophylaxis, a new method to prevent HIV infection where people take a medicine to reduce their risk of becoming infected with HIV. Truvada (emtricitabine/tenofovir disoproxil fumarate), a pill that is taken every day, is currently the only drug that is approved for PrEP, and only for adults.

The US Food and Drug Administration (FDA) has requested that more studies be done to learn information about what happens when teenage girls use the vaginal ring. This study is being done to see if the vaginal ring with the study product, dapivirine, is safe and acceptable to teenage girls like you.

Who will be in this research study?
Healthy teenage girls who are found to be eligible will be enrolled in the study.

What will I be asked to do if I join this research study?
In this study you will have to wear a vaginal ring for 24 weeks, replacing the vaginal ring every 4 weeks. You will also be asked to come to the clinic for 9 study visits (including the visit today). If you agree to join this study, you will be in the study for about 25 weeks. Each visit will take approximately [*Sites to insert the approximate length of time*].

You should know that there are two groups in this study. One group will receive a vaginal ring with the study product, dapivirine, in it. The other group will receive a vaginal ring that looks just like the dapivirine-containing vaginal ring but does not have any study product in it. We call this the placebo vaginal ring. Which vaginal ring you get is decided by chance [*Sites to insert preferred description of 'Randomization'*]. There will be more teenage girls (approximately 72 girls) in the group using the vaginal ring with study product in it than in the group (approximately 24 girls) using the placebo vaginal ring. Neither you nor the staff can decide which group you will be in. Also, neither you nor the staff will know if you are using the vaginal ring with study product or the placebo vaginal ring because both vaginal rings look the same.

What procedures will be performed for research purposes?

Screening Procedures – [*Sites to modify the following section as required by local regulatory authorities to include the specific timing of procedures*]
Your first visit will happen after you read, discuss, understand and sign forms to agree to participate. The procedures done at this visit will take about [*Sites to insert the approximate length of 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, and questions to determine if you are eligible to be in this study
- Study staff will:
  - Perform a physical exam which will include measuring your height, weight, temperature, pulse, blood pressure, and perform other procedures as needed
  - Talk with you about the requirements of the study including, but not limited to:
    - Not having sex for 72 hours before the study visits, if you are currently having sex
    - Not inserting any non-study vaginal products into the vagina for 72 hours prior to each follow-up visit
    - Keeping the vaginal ring in place and not removing it between visits
    - Not using the following for the duration of your study participation and for 5 days prior to enrollment: spermicides, diaphragms, contraceptive vaginal rings, menstrual cups, cervical caps (or any other vaginal barrier method), douches, lubricants not approved for use by this study.
  - Talk with you about birth control and ways to avoid becoming pregnant
    - You will be required to use birth control for at least 30 days before you attend your Enrollment Visit, even if you are not currently having sex. You will be asked to continue to use the same birth control for the duration of your study participation.
  - Test your urine for:
    - Infections
    - Pregnancy
      - If you are pregnant you cannot join this study. If the study is still open after your pregnancy, you can come back here to find out if you are eligible
  - Perform a pelvic examination:
    - The study doctor or nurse will use a speculum to do this exam. A speculum is a plastic or metal tool used to help open the vagina so that the doctor or nurse can examine the vagina and the cervix. They 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 sexually transmitted diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary

- Take a blood sample [*Sites to insert amount*] to test for:
  - Health of your blood, liver and kidneys
  - Infections passed through sex, including HIV
    - You will be told your HIV test result as soon as it is available. You must receive HIV test results to be in the study. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV test results are not clear. In that case, we will do more tests until we know your status for sure. If the test shows that you have HIV, you cannot join the study. However, we will refer you to the medical care and other services that you may need. The study staff will tell you about other studies you may be eligible for, if any.
    - The study staff will talk with you about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex
- Give you male condoms, if you need them
- Give you treatment for urine infections and infections passed through sex, if needed
- Give you referrals for other services, if needed
- Schedule your next visit to enroll in MTN-023/IPM 030, if you are eligible

Results of tests listed above will be available within [*Sites to specify timeframe*] of your visit. The study staff will review your test results when they are available. If the results show you can join the MTN-023/IPM 030 study, the study staff will explain the study again to you and answer any questions you may have.

Enrollment and Follow-up Procedures – [*Sites to modify the following section as required by local regulatory authorities to include the specific timing of procedures*]

If you are found to be eligible, your next visit will be within 56 days of your Screening Visit. The next visit is called the Enrollment Visit. You will receive and begin wearing the vaginal ring at the Enrollment visit. You will have the following study visits and phone calls:

- Enrollment Visit
- 1-Week Follow-up Phone Call
- 2-Week Study Visit
- 4-Week Study Visit
- 8-Week Study Visit
- 12-Week Study Visit
- 16-Week Study Visit
- 20-Week Study Visit
- 24-Week Study Visit
- 25-Week Follow-up Phone Call

Note: The visit schedule may be adjusted if needed.

- You will be asked to avoid inserting the following vaginal products and/or objects into your vagina: spermicides, diaphragms, contraceptive vaginal rings, menstrual cups, cervical caps (or any other vaginal barrier method), douches, or lubricants for the 5 days prior to Enrollment and throughout the duration of study participation.

- You will be asked to receive and reply to phone calls from the study staff. In addition, you will be asked to answer questions about your study product use by text message on a cell phone. You will be reimbursed for each text message session. You will receive text message(s) once a week. Your answer(s) will be private.

- Study staff will:
  - Confirm you are able to join the study and that you understand the study requirements
  - Ask you questions about your vaginal practices
  - Ask you to provide or update information about where you live and how we can contact you
  - Ask if you have had any changes in your health (including what medicines you are taking) and your menstrual periods
  - Describe any health problems or other problems having to do with the study, including the vaginal ring, since your last visit (except at your Enrollment visit)
  - Perform a physical exam at some visits
  - Take a sample of your blood at some visits [Sites to insert amount] to:
    - Test for HIV. You will be told your HIV test result as soon as it is available. You must receive your HIV test results to be in the study. You will talk about the meaning of your results and how you feel about them, and ways to prevent HIV and other STIs. Sometimes HIV test results are not clear. In that case, we will do more tests until we know your results for sure. If the test shows you have HIV, you cannot join the study. We will tell you where you can get care and other services you may need. You will be told about other studies you may be eligible for, if any.
    - Check the health of the blood, liver and kidneys
    - To see how much of the study product, dapivirine, is getting absorbed by your body.
    - Check on the health of your blood, liver and kidneys (these tests may be performed at any visit, if indicated).
  - Test your urine at some visits for:
    - Pregnancy
      - If you are pregnant you cannot join this study. If the study is still open after your pregnancy, you can come back here to find out if you are eligible
    - Infections passed through sex

- A pelvic examination will be performed at some visits:
  - They will check for signs of infection and other problems.
  - They will take some fluids from your vagina using a swab for research purposes only. They will also take some fluids from your cervix using a swab to test for sexually transmitted infections or sexually transmitted diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary. Some of these swabs may be self-collected. If you are uncomfortable collecting the fluid, a study clinician can collect it for you.
  - During some pelvic examinations, a vaginal wash will be performed. The study doctor or nurse will rinse your vagina and cervix with about 2 teaspoons [SITES TO INSERT LOCAL EQUIVALENT] of sterile (very clean) fluid, and then will collect the fluid in a tube for testing. The fluid collected will be used for research purposes only.
- Provide the results of your tests, when available
  - You will receive the results of the local laboratory tests (e.g., pregnancy test, liver and kidney function tests, STI tests), but you will not receive results of research laboratory tests (e.g., tests which will tell the researchers how much study product has been absorbed in your body) done specifically for this study. However, we will be monitoring your health while you are on this study and if there are test results that show you should stop taking the study product, or if there are other concerns, you will be informed right away.
- Give you referrals for other services, if needed
- Provide treatment or referral for treatment for problems that the study staff may find.
- Provide counseling. The study staff will discuss:
  - The rules of the study and how to follow the rules (except at your Final Visit)
  - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to prevent HIV and other infections passed through sex
  - Birth control and ways to prevent getting pregnant (except at your Final Visit)

The information you provide during these counseling sessions will not be shared with anyone.

- Give you male condoms, if needed
- Schedule your next visit/contact (except at your Final Visit)

- You will be asked to use a study vaginal ring; as part of using the vaginal ring you will:
  - Talk with study staff about how to properly wear and use the vaginal ring, including information about wearing the vaginal ring during your period, how to clean the vaginal ring if it falls out, etc.
  - Receive and, if you are able, insert a new vaginal ring at each visit. If you are not able to insert the vaginal ring yourself, a study clinician can help you

- Have an exam to ensure that the vaginal ring is properly inserted, if needed
- Return your vaginal ring to study staff. Study researchers may keep this vaginal ring for additional testing. These tests will help researchers better understand your vaginal ring use.
- In the event that the vaginal ring falls out, you may return to the clinic to have the vaginal ring reinserted if you are uncomfortable doing so yourself. A new vaginal ring will be provided to you, if needed.
- Answer questions about your experience using the vaginal ring, including whether or not the vaginal ring was removed from or fell out of your vagina. You will be asked to answer questions about your vaginal practices. Answer questions about any problems you may have had during your participation in this study. Also, you may be asked questions about vaginal practices that may affect how the study product is absorbed by your body.
- You may be asked to answer questions that may make you uncomfortable, for example, questions about drug use or sexual activity. You may use a computer to answer these questions or a staff member may ask you these questions directly. It is important that you know that study staff will ask you these questions in private and your responses will be kept confidential.
- Provide study staff with information regarding your vaginal ring use and other related questions by replying via text message to study staff. You may also be reminded of your study visits via text message.

- At any time during the study, the following may need to be collected if you are having symptoms of infection, or if clinicians suspect you may have an infection:
  - Have vaginal and/or cervical swabs collected to test for infections
  - Have a blood sample [Sites to insert amount] collected to test:
    - For infections passed through sex
    - For HIV
    - The health of your blood, liver and kidneys
  - Have urine collected to test for:
    - Pregnancy
    - Infection

It may be necessary for you to make additional visit(s) and/or allow for the collection of additional specimens during your study participation to have any of the study procedures listed above repeated in the event of: abnormal results; difficulties in sample shipping, processing, or testing; and/or if you experience any changes in your physical condition.

In-depth Interview Subset:
About 6 teenage girls from each site will participate in the in-depth interview portion of this study. You may be asked to complete an in-depth interview at the Final Clinic

Visit. During this interview, you will be asked to talk about your experience with the vaginal ring, including vaginal ring removal timing, vaginal hygiene, and condom use behavior. Additionally you will be asked about how your vaginal ring use was affected by your home setting, relationships with your friends and/or boyfriend(s) or girlfriends, and your experience with sex if you are currently sexually active. Questions will be asked regarding the ease of use, privacy, adherence support and feasibility of text messaging and computer survey(s). The in-depth interview will take approximately 60 minutes to complete and will be conducted at the Final Study Visit.

What if I become infected with HIV?

Being in this study will not cause HIV infection. However, there is always a chance that through sex or other activities you could become HIV-positive. If you become HIV-positive, you will stop using the vaginal ring, but you will be asked to continue to come for regularly scheduled visits and for some of the study procedures, if you agree. The study staff will support and refer you for medical care and other available services. If you become infected with HIV, it is possible that you could have dapivirine-resistant HIV, which means that your HIV would still be able to survive in the presence of the study product, dapivirine. A blood test will be performed to find out if you have drug resistance. Results of this test will also help determine which medications would be best to treat your HIV. [*Sites to include/amend the following as appropriate:* If you are interested, study staff will inform you of other research studies you may be eligible for.]

It may be necessary, depending on local and national health requirements, for study staff to report diseases, including HIV, identified among study participants. The reportable diseases at this site are [*Sites to insert*]. We must inform the following [*Sites to insert more detailed information regarding who will be informed of the reportable diseases*].

Pregnancy

The vaginal ring with study product and the placebo ring are not birth control and will not prevent pregnancy. Even if you are not currently sexually active, you must agree to use an effective method of birth control (e.g. birth control pills, hormonal-based methods, intrauterine device (IUD), the patch) but you cannot use a vaginal ring for birth control.

We do not know what effect the study products have on pregnancy, including the effect of the study product on the fetuses of females who use the vaginal ring when pregnant. Because of this, pregnant females may not join this study. Females who join the study must agree to use birth control and have scheduled pregnancy tests while in the study.

If you become pregnant during the study, study staff will refer you to available medical care and other services you may need. The study does not pay for this care. You will stop using the vaginal ring, and if you agree, we will ask you to keep

coming here for study visits as originally planned. We will change the study procedures as needed to protect your health while you are pregnant. [*Sites to include/amend the following:* We may also contact you to find out about the health of your pregnancy. We may also contact you about a study that collects information about pregnancy and children up to one year old.] The outcome of your pregnancy is important to study staff; therefore your pregnancy will be followed until the results of your pregnancy are known.

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws

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

Risks of Genital Exams

You may feel discomfort or pressure during the examination of your genital area and inside your vagina. You may have a small amount of vaginal bleeding which will stop shortly after the exam. During the vaginal wash procedure, you may have a temporary cool feeling in your vagina.

Risks of Study Rings

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

- Discharge from the vagina
- Vaginal irritation and discomfort

As with any product that is placed into the vagina, the possibility of toxic shock syndrome exists, although it is very rare. Toxic shock syndrome is a serious but uncommon infection caused by bacteria. While it is unlikely that you should experience toxic shock syndrome as a result of using the vaginal ring, it is important that you alert the study staff if you experience any of the following symptoms: sudden high fever, a faint feeling, diarrhea, headache, a rash, and muscle aches.

Risks of Study Drugs

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

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

Risks of HIV and Sexually Transmitted Infection (STI) Testing
Being tested for HIV and STIs may cause anxiety regardless of the test results. Receiving a positive test result, indicating that you have an HIV infection or an STI, may have a strong emotional impact. When being tested for HIV infection, there is the possibility that you are in the earliest stage of infection and that the HIV test may not be able to detect the infection

Other Possible Risks
You may become embarrassed and/or worried when discussing sexual activities, if you are currently sexually active, ways to protect against HIV and other infections passed through sex, and your test results. You may be worried while waiting for your test results. If you have HIV or other infections, learning this could make you worried or upset. Finding out your HIV status could also cause problems between you and your partner or your family. Trained study counselors will help you with any feelings or questions you have.

We will make every effort to protect your privacy while you are having the study visits, exams, and tests. Your visits will take place in private. Reports via computer or text messages will be stored in computers that are password-protected and will not include personal information that could identify or link information to you; only your study ID number will be recorded. You will be shown how to erase the text message sessions from your mobile phone by study staff. However, as with all text messages sent from and received on your phone, it is possible that others may see your personal messages. Protections have been made to ensure that questions asked via text message are vague and will not directly convey information about your participation in this research study.

If you are chosen for the in-depth interview subset, study staff will talk with you about how and when you used the study products, and they will audio record the discussion using a digital audio recorder. The audio files will be put into writing by the person interviewing you or by another person who does not know you and does not have your personal information. The audio recordings will be destroyed as soon as they have been put into writing; usually this is about three months after your interview. The person in charge at this site will make sure that these records have been destroyed. You should NOT identify anyone in the in-depth interviews. Also, any names that might be mentioned on the recording will NOT be noted. Instead a generic description will be used in the transcript (i.e., if you refer to a friend's name, "FRIEND1" will be noted).

It is possible that others may learn of your participation in this study, and because of this, may treat you unfairly or discriminate against you. For example, you may feel uncomfortable at school, you could have problems getting or keeping a job, or being accepted by your family, friends, or community. It is also possible for you and/or your partner to feel the vaginal ring during sexual activity, if you are currently sexually active. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

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

This study cannot provide you with general medical care, but study staff will refer you to another medical provider who can provide you with care.

You will be counseled and tested for HIV and STIs. 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.

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 vaginal ring may be causing bad side effects, you will be told about this. It is important for you to know that other drugs are being tested to prevent getting HIV. Researchers working on this study will provide you with new information about HIV prevention that becomes available, regardless of the product, if it is found to be effective in adolescent females. You will also be told when study results may be available, and how to learn about them.

A description of this clinical trial is available on http://www.ClinicalTrials.gov, as required by the U.S. law. 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 FDA, US NIH, 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)/ the Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of research participants
- The Study Monitoring Committee (SMC) recommends that the study be stopped early. (A SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study)
- You are not able to keep appointments
- Other reasons that may prevent you from completing the study successfully

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

- You become pregnant
- You become infected with HIV
- You are using PrEP for HIV prevention
- You are using PEP due to HIV exposure
- You are using non-therapeutic injectable drugs
- A study doctor decides that using the vaginal ring would be harmful to you
- You require a treatment that you may not take while using the study vaginal ring
- You have a bad reaction to the study vaginal ring

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

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

ALTERNATIVES TO PARTICIPATION

As previously mentioned, currently the only known way to prevent HIV is through the consistent use of condoms and/or through the use of PrEP.

[*Sites to include/amend the following, if applicable:* There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing and birth control. We will tell you about those places if you wish.]

COSTS TO YOU

[Site to complete according to site capacity] There is no cost to you for study related visits, the vaginal ring, physical examinations, laboratory tests or other procedures. Treatments available to you from the study site for infections passed through sex (other than HIV) 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 will receive [*Sites to insert amount $xx]* for responding to text messages. If chosen to take part in the in-depth interview, you will receive [*Sites to insert amount* $xx]. You may receive *[Sites to insert amount $xx]* for any visits which occur in between your normally scheduled visits.

CONFIDENTIALITY

Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality.

[*Sites to insert details regarding the confidentiality of protected health information and conditions under which the clinician may share protected health information with the participant's parent/guardian*].

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff is required by law to take steps to keep you and others safe. This means that we have to report to the authorities (hospital, police, or social services) any information you tell us that suggests that you might be in danger such as if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you. Also, infectious diseases must be reported to health authorities as required by local law. *[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 *[LOCAL HEALTH AUTHORITY].*

The study staff may use your personal information to verify that you are not in any other research studies. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH
- [*Sites to insert applicable local authorities*]
- IPM, the organization that supplies the vaginal rings
- Study monitors
- Site Institutional Review Board (IRB)/ Ethics Committee (EC), an Ethics Committee is a committee that watches over the safety and rights of research participants
- Study staff

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

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of study participation. This US federally funded study does not have the ability to provide compensation for research-related injury. If you are injured or become ill from taking part in this study, it is important to tell your study doctor. Emergency treatment may be available but you, your parent/guardian, or your insurance company will be charged for this treatment. You do not give up any legal rights by signing this consent form.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

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

PROBLEMS OR QUESTIONS

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

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

[Sites to omit the following if a separate consent for Storage and Future Testing of Specimens is required]

CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION

Please carefully read the statements below and think about your choice. No matter what you decide it will not affect whether you can be in this research study. There might be a small amount of urine, blood, vaginal and cervical fluids left over after we have done all of the study related testing for your study visits. We would like to ask your permission to store your leftover urine, blood, vaginal and cervical fluids, and related health information for use in future studies. If you agree, your samples and related health data will be stored safely and securely. Only approved researchers will have access to the samples. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. There is no time limit on how long your samples will be stored. The specific type of testing planned for these specimens is not yet known, however samples may be used by the MTN Laboratory Center to complete additional quality assurance and control testing, ensuring that the tests perform correctly and supply accurate data. Any future testing, beyond the quality assurance and control testing, will also have to be approved by an Ethics Committee/ Institutional Review Board. No genetic testing (limited or genome-wide) is planned. You can still enroll in this study if you decide not to have urine, blood, vaginal and cervical fluids stored for future studies. You can withdraw your consent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study, and the leftover samples will be destroyed. However, researchers will not be able to destroy samples or information from research that is already underway.

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

_____
Date

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

_____
Date

SIGNATURES- VOLUNTARY CONSENT

[Insert signature blocks as required by the local IRB/EC:]

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions which I have about my rights as a research participant will be answered by [*INSERT LOCAL IRB INFORMATION*]

_____	_____	_____
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

VERIFICATION OF EXPLANATION

I certify that I have carefully explained the purpose and nature of this research to (name of participant) in age appropriate language. She has had an opportunity to discuss it with me in detail. I have answered all of the participant's questions and she provided affirmative agreement (i.e., consent) to participate in this research.

_____

Study Staff's Name Conducting Consent Discussion (Print)

_____	_____
Study Staff Conducting Consent Discussion (Signature)	Date

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