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MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

TABLE OF CONTENTS

MTN-025

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Microbicide Trials Network

Funding Agencies:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
US National Institute of Mental Health
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International Partnership for Microbicides

IND #108,743

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TABLE OF CONTENTS

Table of Figures

MTN-025

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	Antiretroviral
AST	aspartate aminotransferase
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
AUC	area under plasma concentration-time curve
AVAC	Global Advocacy for HIV Prevention
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
CAB	community advisory board
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CBC	complete blood count
CDC	U.S. Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
Cmax	maximum concentrations
Cmin	minimum concentrations
CMRB	Clinical Microbicide Research Branch
CRF	Case Report Form
CROI	Conference on Retroviruses and Opportunistic Infections
CT	Chlamydia trachomatis
CTA	clinical trial agreement
CTU	Clinical trials unit
CWG	Community Working Group
DAERS	DAIDS Adverse Events Reporting System
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAPY	di-aminopyrimidine
DLV	Delavirdine
DNA	deoxyribonucleic acid
EAE	expedited adverse event
EC	Ethics Committee
EC_{50}	50% effective concentration
EFV	efavirenz
FDA	Food & Drug Administration (U.S.)
FHCRC	Fred Hutchinson Cancer Research Center
FTP	File Transfer Protocol
g	Grams
GC	*Neisseria gonorrhoeae*

GCP	Good Clinical Practice
GMP	good manufacturing practices
hCG	human chorionic gonadotropin
HOPE	HIV Open-label Prevention Extension
hu-PBL	human peripheral blood lymphocytes
hu-SCID	human severe combined immunodeficient
HIV-1	human immunodeficiency virus-1
HPTN	HIV Prevention Trials Network
IATA	International Association of Air Transport
IB	Investigator's Brochure
ICF	Informed Consent Form
IDI	in-depth interview
IND	Investigational New Drug
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
ITT	intent-to-treat
IUCD	intrauterine contraceptive device
JHU	Johns Hopkins University
JKUAT	Jomo Kenyatta University of Agriculture and Technology
KOH	potassium hydroxide
LC	Laboratory Center
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantification
LOC	Leadership and Coordinating Center
µg	microgram
µM	micromolar (10^{-3} mol/m^3)
mg	Milligram
mL	Milliliter
MO	Medical Officer
MOP	Manual of Operational Procedures
MTN	Microbicide Trials Network
MU	Makerere University
MU-JHU	Makerere University - Johns Hopkins University
NAAT	nucleic acid amplification test
ng	nanogram per milliliter
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
nM	nanomolar (10^{-6} mol/m^3)
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
PCR	polymerase chain reaction

PEP	post-exposure prophylaxis
pg/mL	picogram/milliliter
PID	pelvic inflammatory disease
PK	Pharmacokinetic
PPD	Pharmaceutical Product Development, Inc.
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PSP	Prevention Sciences Program
PSRT	Protocol Safety Review Team
PTID	participant identification
PUEV	Product Use End Visit
QD	quaque die (once daily)
RNA	ribonucleic acid
RPR	rapid plasma reagin
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SSP	study specific procedure(s)
STI	sexually transmitted infection
TEAE	treatment emergent adverse event
UCSF	University of California- San Francisco
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNC	University of North Carolina
UPMC	University of Pittsburgh Medical Center
USA	United States of America
UTI	urinary tract infection
VR	vaginal ring
WHO	World Health Organization
wt	wild-type

MTN-025

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INVESTIGATOR SIGNATURE FORM

Version 1.0

August 22, 2014

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-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

PROTOCOL SUMMARY

Short Title:	HIV Open-label Prevention Extension (HOPE)
IND Sponsor:	International Partnership for Microbicides
Funders:	Division of AIDS, NIAID, NIMH, NICHD, US NIH
Protocol Chair:	Jared Baeten, MD, PhD
Protocol Co-chairs:	Nyaradzo M. Mgodi, MBChB, MMed Thesla Palanee-Phillips, PhD
Sample Size:	Eligible former MTN-020 participants
Study Population:	Former MTN-020 participants who are HIV-uninfected and not pregnant *Decliner Group: Former MTN-020 participants who decline participation in the main MTN-025 study*
Study Sites:	Approved former MTN-020 sites
Study Design:	Phase 3B, open-label, multi-site, randomized trial Following demonstration of safety and efficacy of the dapivirine vaginal ring in MTN-020, eligible MTN-020 participants will be offered enrollment into MTN-025, a trial designed to obtain additional safety and adherence data in women randomized to monthly vs. quarterly follow-up.
Study Duration:	Approximately 13 months of follow-up per participant with a projected accrual period of approximately 6 months at each site. *Note: In an effort to provide women with the maximum ability to enter the MTN-025 trial, following the formal ~6-month study accrual period participants will continue to be enrolled throughout the duration of the trial, provided that at least 4 months of time on study is supported by the timeline. An adjusted (shortened) follow-up period will be employed for women who enroll after the formal accrual period.*

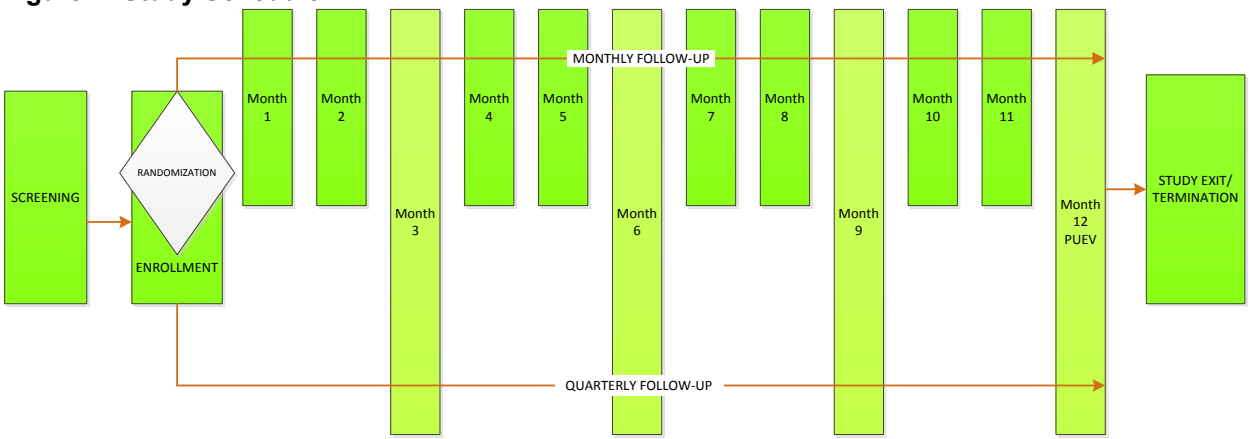
Study Product: Dapivirine VR

Study Regimen: Participants will receive a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine to be replaced each month for a total period of 12 months of use.

MTN-025 participants are to be randomized to one of two types of follow-up:

- Monthly
- Quarterly

Figure 1: Study Schedule



Primary Objectives:

1. Safety
   - To characterize the safety profile associated with the open label use of the dapivirine vaginal matrix ring (25 mg) in women, and to assess safety when randomized to a monthly vs. quarterly follow-up schedule

2. Study Product Adherence
   - To characterize adherence the open label use of the dapivirine vaginal matrix ring (25 mg) in women and to compare adherence when randomized to a monthly vs. quarterly follow-up schedule

Primary Endpoints:

1. Safety
   - Grade 2 adverse events (AEs) judged to be related to the dapivirine vaginal ring
   - Grade 3 and higher AEs
   - All serious AEs

2. Study Product Adherence
   - Residual levels of dapivirine in returned vaginal rings
   - Blood dapivirine levels

Secondary Objectives:

1. Incidence
   - To assess incidence of HIV-1 infection

2. Drug Resistance
   - To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection

Secondary Endpoints:

1. Incidence
   - HIV-1 infection as measured by the protocol algorithm

2. Drug Resistance
   - HIV-1 drug resistance mutations among participants who acquire HIV-1, as measured by standard genotype analysis and more sensitive methods to detect low frequency drug-resistant variants

Exploratory Objectives:

1. To explore participant understanding of efficacy

2. To explore ring acceptability in the context of known efficacy

3. To assess the feasibility of a one-month vs. three-month follow-up schedule

4. To describe the genital microenvironment in women exposed to the dapivirine vaginal ring

5. To characterize the MTN-020 participants who choose not to enroll into MTN-025

Exploratory Endpoints:

1. Understanding of efficacy
   - Self-reported understanding of partial efficacy

2. Understanding of ring acceptability in the context of known efficacy
   - Self-reported product acceptability and attitudes towards combination prevention

3. Feasibility of one month vs. three month follow-up
   - Participant report of product storage issues and feasibility regarding the follow-up schedule
   - Visit retention by arms
   - Proportion of returned rings (used and unused) by arms

4. Genital microenvironment
   - In genital swab samples, candidate biomarkers of safety, adherence and efficacy, HIV exposure and antiretroviral resistance, and genital microflora

5. Characterization of MTN-020 participants who do not enroll in MTN-025
   - Participant report of the factors that led to her decision to decline enrollment into MTN-025

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women
Protocol Number:	MTN-025
Short Title:	HIV Open-label Prevention Extension (HOPE)
Date:	August 22, 2014

1.2 Sponsor and Monitor Identification

Funding Agencies:	US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH) 5601 Fishers Lane Bethesda, MD 20892 USA US National Institute of Mental Health (NIMH) 6001 Executive Boulevard Rockville, MD 20852 USA US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) 6100 Executive Boulevard Bethesda, MD 20892 USA
IND Sponsor:	International Partnership for Microbicides (IPM) 8401 Colesville Road, Suite 200 Silver Spring, MD 20910 USA
Monitor:	Pharmaceutical Product Development (PPD), Inc. 929 North Front Street Wilmington, NC 28401-3331 USA

1.3 Medical Officer

Medical Officer:	Lydia E. Soto-Torres, MD, MPH 5601 Fishers Lane Rockville, MD 20892-9831

1.4 Clinical Laboratories

Laboratory Center:	MTN Laboratory Center (LC) 204 Craft Avenue Pittsburgh, PA 15213 USA
Pharmacology:	MTN Pharmacology LC 600 N. Wolfe Street, Osler 527 Johns Hopkins University Baltimore, MD 21287 USA

1.5 Data Centers

Data Center:	MTN Statistical Data and Management Center (SDMC) Statistical Center for HIV/AIDS Research & Prevention (SCHARP)/Fred Hutchinson Cancer Research Center (FHCRC) 1100 Fairview Avenue N., LE-400 PO Box 19024 Seattle, WA 98109-1024 USA
Qualitative Data Center:	RTI International 351 California Street, Suite 500 San Francisco, CA 94104 USA

1.6 Study Operations

Study Operations:	MTN LOC - FHI 360 359 Blackwell Street, Suite 200 PO Box 21059 Durham, NC 27701 USA

2 INTRODUCTION

2.1 Microbicides and Human Immunodeficiency Virus (HIV) Prevention

In 2012, 2.3 million people became newly infected with HIV and 1.6 million lost their lives to acquired immunodeficiency syndrome (AIDS). Every 60 seconds, a young woman is infected with HIV.[1] According to the Joint United Nations Programme on Human Immunodeficiency Virus-1(HIV)/AIDS (UNAIDS) Global Report, the estimated number of individuals living with HIV is 35.3 million globally. Given the high rates of HIV infection among women, female controlled prevention options remain a global priority. Women and girls continue to be affected disproportionately by HIV in sub-Saharan Africa, where women account for approximately 60% of people living with HIV. *T*he ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.

Unprotected heterosexual intercourse is currently the leading mode of HIV acquisition among women. Correct and consistent use of latex condoms is one proven method of preventing HIV acquisition; however, condoms are widely regarded as inadequate prevention options for women, because many women are unable to negotiate condom use with their partners. The most widely available HIV prevention methods require the consent of the male partner. Thus, developing HIV prevention options that women can use remains a global concern. Vaginal microbicides, which are self-initiated and controlled, offer women a critically needed biomedical prevention tool that will complement existing HIV prevention strategies as well as future products being developed.

With successful proof-of-concept that antiretroviral (ARV)-based microbicides reduce the risk of HIV-1 acquisition, confirmatory work and further trials involving different ARV compounds, various formulations, and different dosing strategies, are required to provide options to end users and to improve upon the level of product effectiveness.

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

Multiple clinical trials have evaluated the safety of dapivirine in VRs, gels and in an oral formulation. These clinical trials support the favorable safety profile and tolerability of dapivirine in general and specifically in vaginal delivery formulations. Initiation of the MTN-025 study of the dapivirine VR will be contingent upon demonstration of the safety and efficacy of the product in the ongoing MTN-020 (ASPIRE) study. The specific level

of effectiveness required to trigger activation of the MTN-025 study will be decided upon following discussions with key stakeholders including regulatory authorities, community representatives, and sponsoring agencies. The MTN-025 protocol will be updated with MTN-020 safety and efficacy data, once available.

2.2 Dapivirine Vaginal Ring (VR)

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.[2]The dapivirine matrix VR is a flexible ring containing 25 mg of drug substance dispersed in a platinum-catalyzed cured silicone matrix. When delivered via VR, dapivirine has demonstrated favorable safety and pharmacokinetic profiles as described below.

Dapivirine was originally developed by Janssen Research and Development (formerly Tibotec Pharmaceuticals Ltd.), a subsidiary of Johnson & Johnson, as an oral ARV compound for treatment of HIV/AIDS and was tested in Phase 1 and 2 clinical trials in more than 200 participants.[3] However, dapivirine is also a promising topical microbicide candidate due to its proven *in vitro* and *in vivo* efficacy and favorable safety profile as well as its physical and chemical properties. Dapivirine has potent activity against wild-type HIV-1 strains and strains harboring different resistance-inducing mutations. Dapivirine's ARV profile is superior to that of several other NNRTI drugs, including nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). Like other NNRTIs, *in vitro* tests have also shown that dapivirine is not active against HIV-2 and has little or no activity against common sexually transmitted infections (STI), therefore, it is not intended for use against HIV-2 or other STIs. Dapivirine does not have any contraceptive properties.[4] Detailed information on dapivirine is available in the Dapivirine VR Investigator's Brochure (IB).[5]

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 vaginal gels and therefore a wealth of information was available on that dosage form. However, the dapivirine silicone elastomer VR has now been prioritized over all other dosage forms for the following reasons:

- Clinical trials have demonstrated sustained delivery of high levels of dapivirine throughout the cervicovaginal vault for up to 1 month;
- Since the ring is able to deliver drug for at least 1 month, the burden of user-dependent adherence is lower than for once daily products;

- Product acceptability studies and the experience gained from marketed VR products have established a high level of acceptance and adherence from women using VR with similar physical characteristics;
- The overall cost for the VR is relatively low;
- Minimal storage space is required for the VR when compared with once daily products.

Summaries of the safety and tolerability of dapivirine orally and vaginally as evaluated in clinical studies by IPM and Tibotec Pharmaceuticals delivered 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 matrix VR in which the drug substance is dispersed in a platinum-catalyzed cured silicone.

2.3 Nonclinical Studies of Dapivirine

2.3.1 *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.[2, 4]

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

Resistance

HIV-1 breakthrough in the presence of dapivirine was initially evaluated in studies in which cells were infected with wild-type HIV-1 laboratory strains at a high multiplicity of infection and in the presence of increasing concentrations of dapivirine. At 40 nM virus

breakthrough occurred between 4 and 7 days, at 200 nM breakthrough occurred between 7 and 10 days and at 1 µM it took up to 30 days to observe virus breakthrough. In all cases, mutations were present. Virus that selected 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.

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

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

Cross-resistance

In comparison with NVP, DLV, EFV and emivirine, dapivirine showed significantly better *in vitro* activity against laboratory and recombinant HIV strains resistant to one or more drugs of the same class. The EC_{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.

2.3.2 Condom Compatibility Studies of Dapivirine

Results from male and female condom compatibility studies, IPM 029 and IPM 033, respectively, are anticipated in 2014.

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); and
- Nitrile condoms with silicone lubricant (female condom).

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

2.4 Clinical Studies

2.4.1 Clinical Studies of Dapivirine Vaginal Rings

To date, 26 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted:

- Seven trials of dapivirine VRs (25 mg and 200 mg loads) in which 234 participants were assigned to dapivirine VRs,
- Eight trials of dapivirine vaginal gel in which 491 participants used dapivirine vaginal gel,
- And, eleven trials of oral dapivirine among 211 participants.[2]

Efficacy and safety results from MTN-020 and IPM 027 and other ongoing (as of Q1 2014) clinical trials, including the adolescent trial (MTN-023/IPM 030) and the post-menopausal trial (MTN-024/IPM 031) will be made available to MTN-025 participants.

Pharmacokinetics

Dapivirine VRs

IPM conducted a 28-day safety and pharmacokinetics (PK) trial (IPM 018) in HIV-uninfected women using tin-catalyzed silicone matrix and reservoir rings containing 25 mg of dapivirine. The rings were found to be generally safe and well-tolerated with a promising drug release profile.[6]

IPM also conducted a 28-day trial (IPM 024) involving 16 healthy, HIV-uninfected, sexually abstinent women, between 18 and 40 years of age. The women were randomly assigned (1:1) to a dapivirine (25 mg) matrix ring or a placebo ring for 28 consecutive days. Post-ring insertion (1.5 hour), quantifiable plasma dapivirine concentrations (lower limit of quantification (LLOQ) = 3.00 pg/mL) were observed.[7, 8] These concentrations showed a gradual increase over time, reaching a mean C_{max} of 355.0 pg/mL by day 7 (median T_{max}).

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

For dapivirine in vaginal fluids quantifiable concentrations (LLOQ = 0.40 ng) were also observed 1.5 hours after ring insertion. Generally, maximum concentrations were reached earlier than in plasma. The highest concentrations were observed in the area near where the ring was placed (mean C_{max}: 79.9 µg/g; median T_{max}: day 3), followed by the cervix (mean C_{max}: 66.6 µg/g; median T_{max}: day 4). Dapivirine vaginal fluid concentrations were well above the reported *in vitro* IC_{50} (50% inhibitory concentration for virus replication) of 0.3 ng/mL in MT4 T cells and the concentration at which greater than 99% inhibition of integrated provirus was observed (3.3 ng/mL) in cervical tissue. On day 28, prior to ring removal, the mean concentrations ($C_{pre\text{-}ring\ removal}$) were 38.6 µg/g, 35.8 µg/g and 13.3 µg/g in the area of the ring, in the cervix and near the introitus, respectively.[7, 9]

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

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

Compared to vaginal fluids, systemic exposure to dapivirine in plasma was low.[7] Plasma concentrations did not exceed 553 pg/mL, while the highest vaginal fluid concentration obtained was 171 µg/g. Data suggest that dapivirine is readily released from the ring and absorbed into the surrounding tissue and bloodstream. Concentrations of dapivirine collected within 4 hours of first ring insertion showed quantifiable plasma (LLOQ = 3.00 pg/mL) and cervicovaginal fluid (LLOQ = 0.4 ng) levels. Interestingly, extending the period the ring was worn from 28 to 35 days resulted in some reductions in cervicovaginal fluid concentrations in the area of the ring (32.4 to 20.3 µg/g) and at the cervix (27.8 to 18.5 µg/g), but were similar at the introitus (10.3 to 9.9 µg/g). These values remained at least 3000 times higher than the *in vitro* 99% inhibitory concentration (3.3 ng/mL) in cervical tissue following challenge with HIV-1_{BaL}.

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
MTN-013/ IPM 026***	Safety and PK in women	United States				12	12
TOTAL			**12**	**18**	**8**	**196**	**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 generally safe and well-tolerated.[9] IPM has conducted a review of aggregate safety information which identifies vaginal candidiasis as a possible adverse drug reaction caused by dapivirine vaginal ring use. The 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).[6] 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).[10] Ten women underwent 7-day exposure to dapivirine Ring-002, and three women used a placebo ring for 7 days. There were no SAEs during the trial and few TEAEs. The trial results showed that the dapivirine ring was safe in healthy participants.

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

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

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.

At least one TEAE was experienced by most participants (81% in the dapivirine ring group, and 86% in the placebo ring group). Metrorrhagia was reported most frequently reported, with a similar incidence observed in the dapivirine ring and placebo ring groups.

At least 10% of participants using dapivirine rings experienced the following TEAEs: gynecological chlamydia infection, urinary tract infection, vaginal candidiasis, and upper respiratory tract infection. Participants in both the dapivirine and placebo ring treatment groups experienced gynecological chlamydia infection at a rate of 16% (22/140). Urinary tract infection was experienced by participants using dapivirine and placebo rings, 13% (18/140) and 10% (14/140), respectively.

Approximately 38% (54/140) of participants in the dapivirine ring group and 42% (59/140) of participants in the placebo ring group reported Grade 1 (mild) TEAEs. Forty-one percent (57/140) of participants in the dapivirine ring group and 37% (52/140) of participants in the placebo ring group experienced Grade 2 (moderate) events.

Grade 3 (severe) TEAEs were experienced by three participants in the dapivirine ring group: tonsillitis (also reported as an SAE), vulvovaginal pruritus (considered possibly related), and increased ALT level. Nine participants in the placebo ring group experienced Grade 3 AEs: bronchiectasis (SAE), peritonsillar abscess (SAE), metrorrhagia, decreased blood phosphorus (two participants), decreased lymphocyte count, neutropenia (considered possibly related), stress, and a suicide attempt (SAE).

One Grade 4 (potentially life-threatening) TEAE occurred in the placebo treatment group: one participant died due to hemopneumothorax, which occurred as a result of physical assault.

No TEAEs were considered by the Investigator as definitely related to ring use during IPM 015. The most commonly observed TEAE that was regarded as possibly or probably related to ring use was metrorrhagia, which was reported for 6% (9/140) of participants using dapivirine rings and 3% (4/140) of participants using placebo rings.

IPM 024, conducted in Belgium, enrolled 16 healthy, HIV-uninfected, sexually abstinent women, between 18 to 40 years of age. The women were randomly assigned to a dapivirine (25 mg) matrix ring or a placebo ring for 28 consecutive days. No SAEs were reported in the dapivirine VR group. No AEs were judged by the investigator to be related to the study agent. Most dapivirine VR group participants, 87.5% (7/8), experienced at least one TEAE. Of the women in the dapivirine VR group who

experienced a TEAE, 50% (4/8) reported headache. 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.

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.

2.5 Prevalence of Primary Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) Resistance Mutations

Recent data on primary NNRTI resistance from a WHO threshold surveillance study conducted between 2005-2009 categorized Kwa-Zulu Natal as having 5-15% NNRTI resistance.[13] MTN-009 found 6.5% NNRTI resistance amongst participants screening for VOICE who were already HIV positive, with 87% of those with NNRTI resistance having HIV-1 with Y181C and/or K103N.[14] In the Stanford University HIV Drug Resistance Database, which compiled data from 12,014 HIV-1 subtype C sequences, and 5831 subtype A & D sequences from treatment-naïve and NNRTI-treated persons, the following was found:[15]

Table 2: Frequency of K103N

	Treatment-Naïve	NNRTI-experienced
Subtype C	1.2%	42%
Subtypes A and D	no data	14%

Table 3: Frequency of Y181C

	Treatment-Naïve	NNRTI-experienced
Subtype C	no data	27%
Subtypes A and D	no data	18-20%

2.6 Behavioral Studies

2.6.1 Acceptability of Dapivirine VR

IPM 011 assessed the acceptability of the dapivirine VR and the placebo VR in 170 women. The trial was conducted across multiple sites in Tanzania and South Africa. The study participants found the ring to be very comfortable (95%), very easy to insert (94%) and remove (92%), and rarely were the rings felt during daily activities. All questionnaire respondents, when asked if they would be willing to use the vaginal ring if shown to be effective for HIV prevention, replied that they would use the VR.[16]

In IPM 015, at Week 12, 97% of African women reported that the dapivirine VR was comfortable and that they were willing to use the VR if it was found to be effective. Women preferred to wear the VR every day (97%) and reported that the ring did not interfere with their daily activities (89%). In terms of the male partner acceptability, 63% of women reported that their partner did not feel the ring during sex. Of those participants who reported that their partner felt the ring, only 1% reported that this might be or definitely was a problem.[11]

2.6.2 Adherence of Dapivirine VR

In IPM 011, 11% of the women experienced expulsions/removal, with the most common reason being 'menses related'. In the majority of cases (64%), the VR was washed and re-inserted.[16]

In IPM 015, perfect adherence was reported by 92% of the female participants. Perfect adherence was defined as never having the VR out for more than an entire day. Of the women who reported that the ring was out, the most common activity for expulsion was urination/defecation. The most common reason reported by participants for VR removal was cleaning. As the study progressed, more women reported removing the VR prior to sexual intercourse, 17% at week 2 and 36% by week 12.[11]

2.7 Rationale for Study Design

2.7.1 Study Design

The dapivirine VR advanced to evaluation in Phase 3 safety and effectiveness trials based on data from preclinical and early clinical safety trials. Upon demonstration of the safety and effectiveness of the dapivirine VR in the MTN-020, implementation of the follow-on trial, MTN-025, will commence.

The primary focus of MTN-025 is the collection of additional adherence and safety data, including the examination of multiple approaches to follow-up and safety monitoring (monthly vs. quarterly). Further, MTN-025 will examine incidence of HIV-1 infection and explore the way in which people adopt this biomedical prevention method and incorporate it into the context of their everyday lives.

While there are many facets to the future roll-out of ARV-based prevention that are worthy of study, including potential impacts on behavior, optimizing drug adherence, and implementation strategies for the public sector, all future approaches must be grounded in an evidence base for safe management of these drugs in healthy populations. MTN-025 will contribute to this evidence base by describing the safety outcomes associated with both monthly and quarterly monitoring schedules for women using an ARV for HIV prevention. Safety data will be forwarded to regulatory entities. Roll-out of ARV-based prevention in the public sector in resource-limited environments will likely require a pharmacovigilance strategy that is less costly and time-consuming than the options described here. MTN-025 will provide valuable information that will help guide the development of those strategies.

MTN-025, the HIV Open-label Prevention Extension (HOPE) trial will provide additional safety and adherence data of dapivirine (25 mg) in a silicone elastomer vaginal matrix ring (Ring-004) when inserted monthly in healthy, HIV-uninfected, not pregnant, sexually active research-experienced women should efficacy be demonstrated in MTN-020.

2.7.2 Incorporating Emergent Effective HIV-1 Prevention Strategies

As of June 2014, the United States was the only country where ARVs (the combination daily oral pill emtricitabine/tenofovir disoproxil fumarate [Truvada®]) are licensed for use as pre-exposure prophylaxis (PrEP). However, as candidate microbicides continue to demonstrate evidence of efficacy, the potential for one or more licensed HIV-1

prevention strategies in sub-Saharan Africa may soon become a reality. The HOPE Protocol Team will follow all relevant national policies regarding HIV-1 prevention and will actively consult with stakeholders in the event that an effective intervention is approved locally. Consultation with target populations, policy makers, governments and other stakeholders will be ongoing throughout the duration of study implementation and participant follow-up by study leadership, Microbicide Trial Network (MTN) Leadership and the MTN Community Working Group (CWG).

3 OBJECTIVES

3.1 Primary Objectives

1. Safety
   - To characterize the safety profile associated with the open label use of the dapivirine vaginal matrix ring (25 mg) in women, and to assess safety when randomized to a monthly vs. quarterly follow-up schedule

2. Study Product Adherence
   - To characterize adherence the open label use of the dapivirine vaginal matrix ring (25 mg) in women and to compare adherence when randomized to a monthly vs. quarterly follow-up schedule

3.2 Secondary Objectives

1. Incidence
   - To assess incidence of HIV-1 infection

2. Drug Resistance
   - To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection

3.3 Exploratory Objectives

1. To explore participant understanding of efficacy

2. To explore ring acceptability in the context of known efficacy

3. To assess the feasibility of a one-month vs three-month follow-up schedule

4. To describe the genital microenvironment in women exposed to the dapivirine vaginal ring

5. To characterize the MTN-020 participants who choose not to enroll into MTN-025

4 STUDY DESIGN

4.1 Identification of Study Design

The MTN-025 trial, HOPE, is a multi-site, open-label, randomized, Phase 3B trial that will be implemented if the dapivirine VR is found to be a safe and an effective HIV prevention method in the MTN-020 trial. Eligible MTN-020 HIV-uninfected participants will be randomized to either a monthly or a quarterly follow-up schedule. The study will compare the safety of and adherence to dapivirine (25 mg) in a silicone elastomer vaginal matrix ring between the two follow-up schedules.

4.2 Summary of Major Endpoints

Primary Endpoints:

1. Safety
   - Grade 2 AEs judged to be related to the dapivirine vaginal ring
   - Grade 3 and higher AEs
   - All serious AEs

2. Study Product Adherence
   - Residual levels of dapivirine in returned vaginal rings
   - Blood dapivirine levels

Secondary Endpoints:

1. Incidence
   - HIV-1 infection as measured by the protocol algorithm

2. Drug Resistance
   - HIV-1 drug resistance mutations among participants who acquire HIV-1, as measured by standard genotype analysis and more sensitive methods to detect low frequency drug-resistant variants

4.3 Description of Study Population

Former MTN-020 participants who are healthy, HIV-uninfected, not pregnant and meet eligibility criteria as described in Sections 5.2 and 5.3

Decliner Group: Former MTN-020 participants who decline participation in the main MTN-025 study and meet eligibility criteria as described in Sections 5.4 and 5.5

4.4 Time to Complete Accrual

The majority of former ASPIRE participants are anticipated to enroll approximately 3-6 months following site activation, see Section 10.4 for additional details.

4.5 Study Groups

Study arms include monthly and quarterly follow-up arms as defined in Table 4.

Table 4: Study Regimen

Group	Group Description	Follow-Up
A	Dapivirine VR, containing 25 mg dapivirine	Monthly
B	Dapivirine VR, containing 25 mg dapivirine	Quarterly

4.6 Expected Duration of Participation

The majority of former ASPIRE participants will complete approximately 13 months of follow-up, see Section 10.4 for additional details.

Visits may be completed within specified windows around target dates. Detailed information regarding visit windows will be described in the MTN-025 SSP Manual.

4.7 Sites

Approved former MTN-020, ASPIRE, sites will participate in MTN-025, HOPE.

5 STUDY POPULATION

5.1 Selection of the Study Population

If safety and efficacy of the dapivirine vaginal ring are demonstrated in MTN-020 (ASPIRE); MTN-025 (HOPE), will be implemented as a follow-on trial. Inclusion and Exclusion Criteria, Sections 5.2 and 5.3, respectively, are used to ensure the appropriate selection of study participants for MTN-025.

Decliner Group: Former MTN-020 participants who decline participation in the main MTN-025 study, and who meet inclusion and exclusion criteria in Sections 5.4 and 5.5, will be invited to complete behavioral assessment(s).

5.1.1 Recruitment

Participants will be recruited from study site cohorts of MTN-020 participants. Efforts will be made by study sites to maintain contact with MTN-020, ASPIRE, participants between the end of follow-up in MTN-020 and the initiation of the MTN-025 trial, HOPE,

to provide MTN-020 study results and information regarding the HOPE study to participants. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use. Site community representatives should advise on these materials before they are submitted to the IRB/EC for review. Community education strategies, including group sessions, may be employed as part of participant/partner outreach.

5.1.2 Retention

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

5.2 Inclusion Criteria

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

1) Previously enrolled in MTN-020 (ASPIRE)

2) Able and willing to provide written informed consent to be screened for and to take part in the study

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

4) HIV-uninfected based on testing performed by study staff at Screening and Enrollment (per applicable algorithm in Appendix II)

5) Using an effective method of contraception at Enrollment, and intending to use an effective method for the duration of study participation; effective methods include hormonal methods (except contraceptive ring); intrauterine contraceptive device (IUCD); and sterilization (of participant, as defined in site SOPs)

6) 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

5.3 Exclusion Criteria

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

1) Study product use permanently discontinued in response to an AE or safety related concern while taking part in the MTN-020 (ASPIRE) trial

2) Per participant report at Screening:
   a) Plans to relocate away from the study site during study participation
   b) Plans to travel away from the study site for more than three consecutive months during study participation

3) Per participant report at Enrollment, currently taking Post-Exposure Prophylaxis (PEP)

   Note: PEP use at Screening is not exclusionary. Participants may be enrolled/randomized after the PEP regimen is complete and a negative HIV test is documented within 56 days of providing informed consent for Screening.

4) With the exception of MTN-020 (ASPIRE), participation in any other research study involving drugs, medical devices, vaginal products, or vaccines, within 60 days of enrollment

5) Is pregnant at Screening/Enrollment or planning to become pregnant in the participant's anticipated study participation period
   Note: A documented negative pregnancy test performed by study staff is required for inclusion; however a self-reported pregnancy is adequate for exclusion from screening/enrollment into the study.

6) Currently breastfeeding

7) Diagnosed with urinary tract infection (UTI), pelvic inflammatory disease (PID), STI or reproductive tract infection (RTI) requiring treatment per WHO guidelines

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

8) At Screening, has a clinically apparent Grade 3 pelvic exam finding (observed by study staff) as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009), Addendum 1-Female Genital Grading Table for Use in Microbicide Studies

   Note: 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.

9) Has any of the following laboratory abnormalities at Screening Visit:
   a) Aspartate aminotransferase (AST) or alanine transaminase (ALT) ≥ Grade 3*
   b) Creatinine ≥ Grade 3*
   c) Hemoglobin ≥ Grade 3*
   d) Platelet count ≥ Grade 3*
   e) Pap result ≥ Grade 3 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009)

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

      Note: Women with a documented normal result within the 12 months prior to enrollment need not have Pap smear during the screening period. Need for a repeat Pap within 6 months does not preclude enrollment prior to that result becoming available.

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

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

5.4 Inclusion Criteria- MTN-025 Decliner Group Only

MTN-025 Decliner Group participants must meet all of the following criteria to be eligible for inclusion in the study:

1) Able and willing to provide informed consent
2) Participated in MTN-020 (ASPIRE)
3) Declines MTN-025 (main) study trial participation
4) Able and willing to perform the Decliner Group study procedures

5.5 Exclusion Criteria- MTN-025 Decliner Group Only

MTN-025 Decliner Group participants who meet the following criteria will be excluded from the study:

1) Has any condition that, in the opinion of the Investigator of Record (IoR)/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

5.6 Co-enrollment Guidelines

As indicated in Section 5.2 and 5.3, participants should not take part in other research studies involving drugs, medical devices, vaginal products or vaccines after the Screening Visit and while taking part in this study. Each site will be responsible for defining procedures for management and prevention of co-enrollment prior to initiation.

Exceptions to this guideline may be made for participants to co-enroll in the following types of studies at the discretion of the IoR/designee:

- Participants may take part in ancillary studies approved by the MTN-025 Protocol Chair
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-positive persons
- Participants who become pregnant may take part in observational studies, including pregnancy registries approved by the MTN-025 Protocol Chair

Should any participant report or should study staff discover concurrent participation in any other study after enrolling in MTN-025, the IoR/designee will consult the Protocol Safety Review Team (PSRT) regarding ongoing product use and other potential safety considerations associated with co-enrollment.

6 STUDY PRODUCT

6.1 Regimen

All participants will receive a vaginal ring containing 25 mg of dapivirine to be worn monthly. One new ring will be inserted each month. Participants will be randomized to either monthly or quarterly follow-up visits.

6.2 Administration

The participant will self-insert the study VR monthly. Study participants will be reminded of proper VR insertion and removal procedures at the Enrollment Visit and as needed at subsequent visits. Details on administration (ring insertion, removal, procedures in the event of expulsion or loss) will be provided in the MTN-025 Study Specific Procedures (SSP) Manual.

6.3 Study Product Formulation

The study VR is an off-white, flexible ring containing 25 mg of dapivirine dispersed in a platinum-catalyzed-cured silicone matrix. The ring dimensions are as follows: 56 mm and 7.7 mm, outer diameter and cross-sectional diameter, respectively.

The ring is designed to provide sustained release of drug over a minimum period of one month.

6.3.1 Dapivirine VR

Dapivirine 0.3125% (w/w) is dispersed in a flexible, opaque, cured silicone VR delivery device. The VR will contain 25 mg of dapivirine. The dapivirine VR optimally should be stored in the site pharmacy at 20°C to 25°C, with excursions between 15°C to 30°C.

6.4 Supply and Accountability

6.4.1 Supply

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

6.4.2 Study Product Dispensing

Study VRs are dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. Dispensing takes place on the day of enrollment and at each scheduled follow-up visit, except at the Product Use End Visit and Study Exit/Termination Visit.

Participants randomized to monthly follow-up visits will receive a new ring at each visit. If the participant is unable to attend her next scheduled visit it is up to the discretion of the IoR to provide an additional ring(s). All such circumstances must be documented fully by the IoR/designee as described in the MTN-025 SSP Manual.

Participants randomized to quarterly follow-up visits will be dispensed three rings at each study visit or the option of returning to the site pharmacy or the clinic (based on site dispensing capacity) to obtain a new vaginal ring each month. Participant's preference regarding product dispensation and their choice will be documented.

The pharmacist will only dispense one ring per month or up to three rings per quarter depending on the participant's regimen. If a participant requires an additional ring for any reason, at a time other than when she is scheduled to receive one, she will be required to attend the clinic for an interim visit.

6.4.3 Accountability

Each CRS Pharmacist of Record (PoR) is required to maintain a complete record of all study product received and subsequently dispensed. All unused study products must be returned to the MTN Pharmacist after the study is completed or terminated unless otherwise instructed by the MTN Pharmacist. The procedures to be followed are provided in the MTN-025 Pharmacist Study Product Management Procedures Manual.

All study product dispensed to a participant must be documented by the clinic staff when it is returned. This includes ring(s) 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

As per Section 9, study product use for a participant may be temporarily held or permanently discontinued. Study product must be retrieved within 24 hours and returned to the clinic when product use is permanently discontinued for HIV seroconversion or held temporarily due to potential HIV seroconversion (see Table 5 below). Additional study product retrieval specifications in response to product holds, discontinuations for other reasons, or IoR discretion, can be found in the table below. Study product retrieval may occur either by the participant returning the VR (used and unused) to study staff within the specified timeframe or by study staff conducting outreach to retrieve the product from the participant (e.g., at her home).

Table 5: Retrieval of Study Product

Condition	Timeframe for Retrieval
• Permanent discontinuation due to HIV seroconversion • Temporary hold due to potential HIV seroconversion	Within 24 hours
• Permanent discontinuation for any other reason or IoR discretion • Temporary hold due to pregnancy	Within 5 working days
• Temporary hold for reasons other than pregnancy with expected duration of more than 7 days	Within 7 working days

If product has not been retrieved within the timeframe specified in the table above, 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, to protect participant safety, study product(s) may be retrieved from participants 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 due to seroconversion, pregnancy or other safety related concerns, if the study product(s) are not retrieved within timeframe noted, the MTN-025 PSRT must be informed.

For each participant, all VRs remaining in the participant's possession should be retrieved at the Study Exit/Termination Visit. If the participant does not bring her remaining VR(s) to this visit, study staff must arrange to retrieve the ring(s) within 5 business days.

The PoR will document all unused product returns and store returned unused study products in designated areas within the study pharmacy.

6.5 Concomitant Medications

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

6.6 Use of Intravaginal Medications and Practices

Concomitant use of devices such as diaphragms, menstrual cups, and cervical caps, will be discouraged. Use of contraceptive VRs is prohibited. Products and practices including the use of spermicides, vaginally applied medication, douches, lubricants, tampons, etc., are permitted. Use of intravaginal medications and practices will be captured.

6.7 Condoms

All participants will be offered male condoms. Condoms are highly effective in preventing the sexual transmission of HIV and reducing the risk other STIs, including infections transmitted by genital secretions, and to a lesser degree, genital ulcer diseases.[17-19]Study staff may also offer guidance on the use of the female condoms upon participant request, see SSP for additional details.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is provided in Appendix I. Follow-up study visits may take place on-site, in a participant's home, or at other community-based locations, depending on site capacity and site/participant preference. If genital symptoms are reported during an off-site visit, the participant is instructed to report to the on-site clinic for a clinical evaluation. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites (including the conduct of off-site study visits) are provided in the MTN-025 Study Specific Procedures (SSP) Manual available at http://www.mtnstopshiv.org/studies.

7.1 Pre-Screening

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

7.2 Screening Visit

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

Table 6: Screening Visit

Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent for screening • Assign a Participant Identification (PTID) Number • Assess eligibility • Collect locator information • Provide reimbursement for study visit • Schedule next visit*
Behavioral		• Provide counseling – Contraceptive – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Obtain medical and menstrual history • Obtain concomitant medications • Conduct a physical examination • Perform a pelvic exam • Offer contraceptives*† • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – human chorionic gonadotropin (hCG) – Nucleic Acid Amplification Test (NAAT) for GC/CT – Urine culture*†‡
	Blood	• Collect blood – HIV-1 serology – Complete blood count (CBC) with platelets – Chemistries – Syphilis serology
	Pelvic	• Collect pelvic specimens – Rapid test for Trichomonas – Pap smear interpretation*
Study Product/ Supplies		• Offer condoms

* if indicated; ‡† per local standard of care

7.3 Enrollment Visit (Day 0)

The Enrollment Visit must be completed within 56 days of the Screening Visit.

Note: All enrolled participants will receive regular individual HIV counseling, condoms (if participant is willing to accept them), risk reduction counseling, and treatment for STIs as part of their clinic visits. If other new prevention strategies are found to be efficacious and are incorporated into the national HIV prevention policies, study participants will be counseled about these interventions, and either be offered these interventions by the site or referred to local centers with appropriate expertise, in accordance with WHO/UNAIDS guidelines and local practice and stakeholder consultation.

Table 7: Enrollment Visit

Enrollment Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent for enrollment • Reassess and confirm eligibility • Review/update locator information • Randomization • Provide reimbursement for study visit • Schedule next study visit*
Behavioral		• Conduct behavioral assessment • Provide counseling – Contraceptive – HIV/STI risk reduction – HIV pre- and post-test – Protocol adherence
Clinical		• Update medical and menstrual history • Update concomitant medications • Disclose available test results • Perform a physical examination* • Perform a pelvic exam* • Offer contraceptives* • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – Urine culture* ǂ† – NAAT for GC/CT* †
	Blood	• Collect blood – Plasma archive – HIV-1 serology
	Pelvic	• Collect pelvic specimens – Vaginal fluid (self-collected) – Rapid test for Trichomonas*¶
Study Product/Supplies		• Offer condoms • Provision of study VR use instructions • Provision of study VR(s) • Insertion of one study VR • Digital exam by clinician to check VR placement*

* if indicated; ǂ¶ per local standard of care

7.4 Follow-up Visits

7.4.1 Months 1, 2, 4, 5, 7, 8, 10, 11

Procedures listed below will occur at study months 1, 2, 4, 5, 7, 8, 10, 11 for participants randomized to the monthly follow-up arm.

Table 8: Follow-up Visits: Months 1, 2, 4, 5, 7, 8, 10, 11

Follow-up Visits: Months 1, 2, 4, 5, 7, 8, 10, 11		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit
Behavioral		• Provide counseling (modified, if necessary) – Contraceptive – Protocol adherence – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Review/update medical and menstrual history • Disclosure of available test results • Record/update AEs • Review/update concomitant medications* • Offer contraceptives*¶ • Perform a physical examination* • Perform a pelvic examination* • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – NAAT for GC/CT*† – Urine culture*†Ŧ†
	Blood	• Collect blood – HIV-1 serology – Chemistries* – Syphilis serology*
	Pelvic	• Collect pelvic specimens – Vaginal fluid (self-collected) – Rapid test for Trichomonas*
	Study Product	• Adherence assessment(s): Returned study VR
Study Product/Supplies		• Offer condoms • Removal and collection of used/unused study VR • Provision of VR use instructions* • Provision of study VR • Digital exam by clinician to check VR placement*

* if indicated; Ŧ¶ per local standard of care¶

7.4.2 Months 3, 6, 9

Participants in both study arms will undergo the following procedures quarterly.

Table 9: Follow-Up Visits: Months 3, 6, 9

Follow-up Visits: Months 3, 6, 9		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit
Behavioral		• Conduct behavioral assessment • Conduct social harms assessment • Provide counseling (modified, if necessary) – Contraceptive – Protocol adherence – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Perform physical examination (mandatory at Month 6, if indicated at other visits) • Disclosure of available test results • Record/update AEs • Perform a pelvic examination* • Offer contraceptives* • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – NAAT for GC/CT (mandatory at Month 6, if indicated at other visits) – Urine culture*†
	Blood	• Collect blood – HIV-1 serology – Plasma – Chemistries* – Syphilis serology*
	Pelvic	• Collect pelvic specimens – Vaginal fluid (self-collected) – Rapid test for Trichomonas (mandatory at Months 6 only, if indicated at other visits)
	Study Product	• Adherence assessment(s): Returned study VR
Study Product/Supplies		• Offer condoms • Removal and collection of used/unused study VR(s) • Provision of VR use instructions* • Provision of study VR(s) • Digital exam by clinician to check VR placement*

* if indicated; † per local standard of care

7.4.3 Product Use End Visit (PUEV)

Participants in both study arms will undergo the following procedures at Month 12.

Table 10: PUEV: Month 12

PUEV: Month 12		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit
Behavioral		• Conduct behavioral assessment • Conduct social harms assessment • Provide counseling (modify, if necessary) – Contraceptive – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Perform a physical examination • Perform a pelvic examination • Disclosure of available test results • Record update AEs • Offer contraceptives*† • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – NAAT for GC/CT – Urine culture*†~~‡~~†
	Blood	• Collect blood – HIV-1 serology – Syphilis serology – Chemistries – CBC with platelets – Plasma
	Pelvic	• Collect pelvic specimens – Vaginal fluid (self-collected) – Rapid test for Trichomonas
	Study Product	• Adherence assessment(s): Returned study VR
Study Product		• Offer condoms • Removal and collection of used/unused study VR

* if indicated; ~~‡~~† per local standard of care

7.4.4 Study Exit/Termination Visit

The Study Exit/Termination Visit is to be scheduled approximately 4 weeks after the PUEV.

Table 11: Study Exit/Termination Visit

Study Exit/ Termination Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit*
Behavioral		• Conduct behavioral assessment • Provide counseling – Contraceptive* – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Disclosure of available test results • Record/update AEs • Offer contraceptives* • Perform a physical examination* • Perform pelvic examination* • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – NAAT for GC/CT*† – Urine culture*†‡
	Blood	• Collect blood – HIV-1 serology – Plasma
	Pelvic	• Collect pelvic specimens – Vaginal fluid (self-collected) – Rapid test for Trichomonas*
Study Product		• Offer condoms

* if indicated; ‡† per local standard of care

7.5 MTN-025 Decliner Group

7.5.1 MTN-025 Decliner Group: Screening and Enrollment Procedures

Former ASPIRE participants who decline or express no interest in joining the main MTN-025 trial, may opt to take part in the MTN-025 Decliner Subset. Multiple visits may be conducted to complete all required procedures, as necessary. See Section 7.8, *Behavioral Evaluations* for additional details.

Table 12: Screening and Enrollment Procedures

Screening and Enrollment	
Component	**Procedures**
Administrative and Regulatory	• Confirm eligibility • Obtain written informed consent • Collect demographic data • Provide reimbursement for study visit
Behavioral	• Administer behavioral assessment • Conduct in-depth interview (IDI)*

*=if indicated

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

7.6.1 Participants Who Become Infected with HIV

Participants who become infected with HIV are offered the option to continue follow-up visits per their original study schedule until their originally scheduled study exit date. All participants who become infected with HIV while on study product will be offered enrollment in MTN-015, the MTN Seroconverter Study. Participants are offered enrollment in MTN-015 (http://www.mtnstopshiv.org/studies) at the visit when seroconversion confirmation test results are discussed with the participant.

For those participants who choose to be maintained in MTN-025 follow-up, regardless of co-enrollment in MTN-015, protocol-specified procedures for MTN-025 will continue, except the following:

- HIV serology, HIV pre- and post-test counseling
- Provision of VR, instructions, product adherence counseling
- Complete blood count
- Chemistries
- Scheduled HOPE Study Exit/Termination Visit

For participants who delay or decline enrollment in MTN-015, the following procedures are being completed as part of the MTN-025 study; these procedures are discontinued immediately if the participant enrolls in MTN-015:

- Plasma collection
- CD4+ T cell count
- HIV-1 RNA PCR
- HIV-1 Genotyping (standard resistance testing)

The aforementioned procedures are performed at the following time points:

- Plasma collection, CD4+ T cell count and HIV-1 RNA PCR will be performed upon each instance of a positive HIV rapid test(s) during follow-up
- Plasma collection, CD4+ T cell count and HIV-1 RNA PCR will be performed at the clinic visit immediately following confirmation of an HIV-infection and every three months thereafter for the remaining follow-up period, or as indicated
- HIV-1 Genotyping (standard resistance testing) will be performed on the stored plasma closest to the time of confirmed HIV-1 infection. It may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center.

Please reference the SSP for additional details (http://www.mtnstopshiv.org/studies).

7.6.2 Participants Who Become Pregnant

All protocol-specified study procedures will continue except the following:

- Provision of VR, product use instructions, and adherence counseling. Product use may be resumed after birth or other termination of the pregnancy, as evidenced by a negative pregnancy test performed by study staff, provided the participant is not breastfeeding. VR use should not be resumed earlier than 2 weeks after a 1st trimester loss, or earlier than 4 weeks after 2nd trimester (or later) pregnancy loss or delivery. A pelvic exam must be performed prior to resumption to confirm the absence of any findings that would contraindicate resumption, in the opinion of the IoR/designee.
- Pelvic examination as well as associated procedures, and vaginal fluid collection, after 24 weeks of pregnancy, unless the participant indicates comfort with continuing vaginal procedures post 24 weeks. See SSP Manual for additional guidance.

A participant who becomes pregnant during the course of study participation may be offered participation in MTN-016, the Prevention Agent Pregnancy Exposure Registry.

7.6.3 Participants Who Temporarily Hold or Permanently Discontinue Study Product Use

All protocol-specified study procedures will continue except the following:

- Provision of VR, product use instructions, and adherence counseling

In the event that a participant permanently discontinues study product early, the Adherence and Acceptability Assessments will be administered according to guidance provided from the protocol team. See the MTN-025 SSP Manual for additional guidance.

Guidance related to permanent discontinuation of study product, including consultation with the PSRT, is included in Section 9.

7.6.4 Interim Visits

Interim visits may be performed at any time during the study, for the following or other reasons:

- For administrative reasons, e.g., a participant may have questions for study staff, or may need to re-schedule a follow-up visit.
- For product-related reasons, including to provide participants with a replacement or additional vaginal ring.
- In response to AEs and/or SAEs. When interim contacts or visits are completed in response to participant reports of AEs and/or SAEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care (see also Section 9).
- For interim STI counseling and testing in response to STI symptoms.
- For interim HIV counseling and testing in response to participant report of symptoms consistent with acute seroconversion or presumed exposure to HIV
- To provide participants with the results of confirmatory HIV test results, per the algorithm in Appendix III.
- For other reasons at participant request, e.g., social harm.

All interim contacts and visits will be documented in participants' study records and on CRFs, if applicable.

7.7 Final Contact

Since participants' Study Exit/Termination Visit include laboratory testing for HIV, a final contact may be required to provide her additional study test results, and post-test counseling, if needed. In addition, for participants who become pregnant during study participation, an additional contact may be required to ascertain the participant's pregnancy outcome. Study sites may complete these contacts at the study site or at

community-based locations, depending on site capacities and site and participant preferences. All final contacts will be documented in participant study records.

7.8 Behavioral Evaluations

The following attitudes and behaviors, including the endpoints to assess exploratory objectives, will be assessed either via Audio Computer-Assisted Self Interviewing or CRFs. Additionally, a subset of eligible participants at selected sites will be asked to participate in in-depth interviews and/or focus group discussions (IDI and/or FGDs) at a predetermined time point. These will be conducted by trained interviewers/facilitators to gain further insight on the following behavioral and attitudinal issues:

- Attitudes and understanding of VR efficacy
- VR acceptability and attitudes towards combination prevention (i.e., use-related attributes and preferences, access, cost, health system delivery)
- Motivations for joining or declining participation in research study
- Reports of products storage and use
- Perceived feasibility of study visit regimen
- Sexual activity, including condom use
- Vaginal practices

MTN-025 Decliner Group

Former ASPIRE participants who decline or express no interest in joining the MTN-025 trial either prior to screening or prior to enrollment, will be invited to complete behavioral assessment(s), which may include IDI(s) to explore reasons for disinterest.

7.9 Adherence Counseling

Study product adherence counseling will be provided as a component of the Protocol Adherence Counseling 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.

7.10 Clinical Evaluations and Procedures

Physical exams will include the following assessments:

- General appearance
- Weight
- Vital signs
    - Temperature
    - Pulse

  - Blood pressure
  - Respirations
- Abdomen
- Height*
- Lymph nodes*
- Neck*
- Heart*
- Lungs*
- Extremities*
- Skin*
- Neurological*

**may be omitted after the Screening Visit*

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

The required sequence of procedures and specimen collection performed during pelvic exams will be specified in the MTN-025 SSP Manual.

Participants for whom there is documentation of surgical sterilization may have contraceptive counseling omitted, in accordance with any relevant site SOPs.

7.11 Laboratory Evaluations

Local Laboratory

- Urine
  - hCG
  - NAAT for GC/CT
  - Culture (per local standard of care)
- Blood
  - Plasma archive (stored at site until notified by MTN Laboratory Center (LC))
  - Plasma (stored at site until notified by MTN LC)
  - Syphilis serology
  - HIV serology
  - CBC with platelets
  - Chemistries
    - Creatinine, AST, ALT
- Pelvic
  - Rapid test for Trichomonas
  - Vaginal fluid

Laboratory Center

- Blood
  - HIV-1 confirmatory testing as needed (see Appendix III)
  - Drug concentration in blood
  - HIV drug resistance

- Pelvic
  - Vaginal fluid for candidate biomarkers of safety, adherence and efficacy, HIV exposure and antiretroviral resistance, and/or genital microflora, as needed

IPM or MTN Designated Laboratory:

- Study Product- Vaginal Ring
  - Adherence assessment(s)

7.12 HIV Infection (Secondary Endpoint) Determination

All study sites will perform HIV testing per the algorithm in Appendix III for purposes of secondary endpoint determination. Prior to study initiation, all sites will have validated this algorithm in accordance with the policies described in the MTN Manual of Operations (MOP) (http://www.mtnstopshiv.org/node/187). All sites will participate in ongoing proficiency testing of their HIV testing procedures throughout the course of the study. The HIV test kits used at each site are pre-approved by the MTN Laboratory Center (LC); at each testing time point when rapid tests are used at least one FDA-approved rapid test kit is used. All confirmatory testing is performed using FDA-approved test kits.

HIV DNA is not routinely used in MTN-025 for HIV diagnosis but may be used when requested by the MTN LC.

The MTN LC will verify HIV testing performed at the study site laboratories for purposes of eligibility determination and secondary endpoint ascertainment as follows:

- The MTN LC will test Study Entry, PUEV, and scheduled Termination Visit specimens from a 10% random sample of participants enrolled at each site for evidence of HIV infection using FDA-licensed tests. Study Entry specimens are collected at participants' Enrollment Visits. If any false-negative local laboratory results are identified, the LC will test the respective Study Entry, PUEV and scheduled Termination Visit specimens from all enrolled participants from that Clinical Research Site.

- The MTN LC will test the Study Entry and Seroconversion specimens from all study participants identified by the local laboratories as having become infected with HIV during the study follow-up period. The LC will also test matched Study Entry and Follow-Up specimens from a random sample of uninfected participants (equal to the number of seroconversions). Study Entry specimens are collected

at participants' Enrollment Visit. Seroconversion specimens are collected at the schedule specified in Section 7.6.1. All specimens will be tested for evidence of HIV infection using FDA-licensed tests. For all seroconverters, Study Entry specimens also will be confirmed.

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

In addition to all of the above, an endpoint adjudication committee will provide guidance on endpoint determination to the Protocol Team on an as needed basis. See the MTN MOP (http://www.mtnstopshiv.org/node/187) for detailed information on the composition, roles, and responsibilities of the endpoint adjudication committee.

7.13 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical laboratory practice (http://apps.who.int/tdr/publications/tdr-research-publications/gclp-web/pdf/gclp-web.pdf), in accordance with current US Division of AIDS (DAIDS) Laboratory Requirements, MTN-025 Study Specific Procedures Manual (http://www.mtnstopshiv.org/studies) and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to standardize procedures. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System. In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

7.14 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)

7.15 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 U.S. Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH). All biological specimens will be transported using packaging mandated by US Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazard waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

Site IoRs/designees are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Co-Chairs, DAIDS Medical Officer, Protocol Safety Physician(s), and SDMC Clinical Affairs Safety Associate will serve as the Protocol Safety Review Team (PSRT). The MTN SDMC prepares routine AE and clinical data reports for review by the PSRT, which meets via conference call approximately once per month or as needed throughout the period of study implementation to review safety data, discuss product use management, and address any potential safety concerns.

8.2 Clinical Data Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are the first layer of this tiered system and 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.

During the trial, the PSRT will review safety reports and conduct calls to review the data as appropriate. The content, format and frequency of the safety reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to these routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary,

experts external to the MTN with expertise in the fields of microbicides, biostatistics, or medical ethics may be invited to join the PSRT safety review.

After the product use and the final safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the MTN-025 PSRT.

A Study Monitoring Committee (SMC) has study oversight and is charged with reviewing participant safety data as no Data Safety Monitoring Board (DSMB) is planned for this study, see Section 10.7.1 for additional details.

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 both groups beginning at the time of enrollment (i.e., once a participant is randomized). The term “investigational product” for this study refers to the vaginal ring.

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

Study site staff will document in source documents all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product.

Study staff will also report on CRFs the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs, including STIs
  - Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs

  - Genital bleeding clinically assessed to be expected is not an AE
- All AEs of severity Grade 2 or higher
- All serious AEs
- All AEs that result in permanent discontinuation of study product use
- All lab test abnormalities specified in the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), that are not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements per Section 8.3 below; this includes all congenital anomalies identified in the fetuses and/or infants of study participants

AE severity and laboratory tests will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), except that asymptomatic BV and asymptomatic candidiasis will not be reportable AEs. In cases where a genital AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the exit visit, the status/outcome of the AE should be updated to “continuing at end of study participation” and the AE Log form should be re-faxed to SCHARP DataFax. For any serious or expedited AEs (SAEs/EAEs) that are continuing at a participant’s study exit visit, the IoR/designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the SAE/EAE must be re-assessed by study staff 30 days after the participant’s study exit visit; additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the study exit visit. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The PSRT may advise study staff as to whether any additional follow-up may be indicated on a case by case basis. For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE Log CRFs based on the re-assessments.

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
- *Not Related:* There is not a reasonable possibility that the AE is related to the study agent

8.4 Expedited Adverse Event Reporting Requirements

8.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/. For each study participant, expedited AE reporting will be undertaken throughout the scheduled duration of follow-up, i.e., from the time of random assignment through study termination.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov 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 agent for which expedited reporting is required is the dapivirine VR
- For all SAEs submitted, sites must file an initial report and an update to IPM and the DAIDS Medical Officer with the final or stable outcome unless the initial SAE submitted had a final or stable outcome noted already

8.4.3 Grading Severity of Events

The grading of severity of events and the reporting period will be the same as for all AEs, as described in Section 8.3.1. The most current Division of AIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification, August 2009) and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification, 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 final study visit (Study Exit/Termination Visit).
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.5 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the PSRT and responsible site ECs/IRBs according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Each site will provide such care and counseling in accordance with standardized guidance provided in the MTN-025 SSP Manual. While maintaining

participant confidentiality, study sites may engage their community advisory boards (CABs) in exploring the social context surrounding instances of social harm.

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 ECs/IRBs in accordance with ECs/IRB requirements.

9 CLINICAL MANAGEMENT

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

9.1 Grading System

AE severity grading is described in Section 8.3.3.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

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

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

- Acquisition of HIV infection; such participants will not resume product use at any time. The study VR should be held beginning immediately upon recognition of the first reactive rapid HIV test. If via the algorithm in Appendix III the participant is determined to be HIV-uninfected, she may resume product use. The IoR/designee must permanently discontinue the study VR if HIV infection is confirmed.
- Allergic reaction to the study VR.

A participant will be temporarily held from study VR for any of the following reasons:

- A reactive rapid HIV test.
- Pregnancy. A participant who becomes pregnant may resume product use after giving birth or other pregnancy outcome, as evidenced by a negative pregnancy test performed by study staff, provided the participant is not breastfeeding. A pelvic exam must be performed prior to resumption to confirm the absence of any findings that would contraindicate resumption, in the opinion of the IoR/designee.
- Breastfeeding. Product use may resume when the participant reports complete cessation of breastfeeding.
- Report of use of PEP for HIV exposure. The participant may resume product use when she reports completion of PEP and is confirmed HIV-uninfected based on testing performed at the study site per the algorithm in Appendix III.
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee. The IoR/designee must consult the PSRT on all temporary product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation. If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time.

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

Grade 1 or 2

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

Grade 3

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

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

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

9.5 Other Clinical Findings

The IoR/designee should manage STI/RTI per local guidelines or current WHO guidelines, available at http://www.who.int/en/.

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. Observed single dose treatment should be provided whenever possible, per clinician discretion. When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible.

- Study VR need not be 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 hold is warranted, consultation with the PSRT is required.

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

Management of genital events observed at scheduled or interim visits will be in accordance with the following:

Superficial epithelial disruption (abrasion/peeling)

- Continue study VR use
- Perform naked eye evaluation
- Re-evaluate by speculum examination in 3-5 days
- If condition worsens, temporarily hold study VR use and consult the PSRT; otherwise continue study VR use

Deep epithelial disruption (ulceration)

- Temporarily hold study VR for deep epithelial disruption confirmed by site investigator
- Re-evaluate in 3-5 days and resume study VR use if resolved
- If unresolved at 3-5 days, re-evaluate within 2-3 days. If resolved at that time, may resume study VR use. If unresolved at this second reevaluation, continue

temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard
- If there is reoccurrence with no identified etiology, continue temporary product hold and consult the PSRT regarding permanent discontinuation

Localized erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface
- Continue study VR use
- Perform naked eye evaluation
- If asymptomatic, re-evaluate at next regularly scheduled visit
- If symptomatic, re-evaluate by speculum examination in 3-5 days
- If worsened significantly, temporarily hold study VR use and consult the PSRT; otherwise continue study VR use

Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema
- Temporarily hold study VR
- Perform naked eye evaluation
- Re-evaluate in 3-5 days and resume study VR use if resolved
- If unresolved at 3-5 days, re-evaluate within 2-3 days. If resolved at that time may resume use. If unresolved at this second reevaluation, continue temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard

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

Cervicitis (including findings on exam such as inflammation and/or friability)
- Temporarily hold study VR
- Evaluate for GC/CT; consider syndromic management, pending results of testing and per clinician discretion
- If GC/CT detected, provide or prescribe treatment
- Reevaluate in 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
- Further evaluation or treatment per clinician discretion

Genital ecchymosis
- Continue study VR use

- Perform naked eye evaluation
- Further evaluation or treatment per clinician discretion

The study product 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, notification of the PSRT is required.

9.6 HIV Infection

A participant who has a positive test for HIV must have study product held, but will not be withdrawn from the study. If the participant is subsequently determined to be HIV-uninfected according to the algorithm in Appendix III, study product may be resumed. If HIV infection is confirmed, study product will be permanently discontinued by the IoR/designee. Participants identified as infected with HIV are managed or referred for management according to the local standard of care. These participants are also offered participation in MTN-015, the MTN Seroconverter Study, which also includes provisions for the clinical management and/or referral of participants infected with HIV.

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

At every study visit, study staff will actively follow-up on prior referrals to HIV care and support services, to determine whether the participant sought the care to which she was referred, the outcome of the referral, and whether additional referrals are needed. All follow-up actions, outcomes, counseling, and plans for next steps are documented in participant study records. Results of study laboratory testing may be helpful in clinical management; these results are provided to the participant and her medical provider as soon as they are available.

9.7 Pregnancy

A participant who becomes pregnant at any time during the study must have study product temporarily held, but will not be withdrawn from the study. Every effort will be made to have the study participant continue in modified follow-up until her study termination visit or pregnancy outcome is ascertained. 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.

Participants who become both pregnant and HIV-infected will have expedited HIV-1 resistance testing performed at the MTN LC to provide information about possible resistance that might impact the efficacy of ART regimens to reduce mother-to-child HIV-1 transmission. The participant will be referred to local providers for antenatal care, and prevention of mother-to-child transmission services. HIV testing for infants is provided by the study if not otherwise accessible by the participant.

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

All pregnancies will be followed until a pregnancy outcome can be ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). This includes participants who are pregnant at the Study Exit/Termination Visit. Pregnancy outcomes are reported on relevant CRFs.

9.8 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. The PSRT must be notified of all terminations conducted per IoR discretion. Participants also may be withdrawn if the study sponsors, 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 will be 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 Phase 3B, open-label, multi-site, randomized trial. A sample size of approximately 1000-2500 participants will be randomly assigned in a 1:1 ratio to either monthly or quarterly follow-up. The two main goals of the trial are:

1. To characterize the safety profile associated with the open label use of the dapivirine vaginal matrix ring (25 mg) in women, and to assess safety when randomized to a monthly vs. quarterly follow-up schedule

2. To characterize adherence the open label use of the dapivirine vaginal matrix ring (25 mg) in women and to compare adherence when randomized to a monthly vs. quarterly follow-up schedule

Secondary objectives of the study include assessing the incidence of HIV-1 infection and frequency of HIV-1 drug resistance in women who acquire HIV-1 infection.

10.2 Study Endpoints

10.2.1 Primary Endpoints

1. Safety
   - Grade 2 AEs judged to be related to the dapivirine vaginal ring
   - Grade 3 and higher AEs
   - All serious AEs

2. Study Product Adherence
   - Residual levels of dapivirine in returned vaginal rings
   - Blood dapivirine levels

10.2.2 Secondary Endpoints

1. Incidence
   - HIV-1 infection as measured by the protocol algorithm

2. Drug Resistance
   - HIV-1 drug resistance mutations among participants who acquire HIV-1, as measured by standard genotype analysis and more sensitive methods to detect low frequency drug-resistant variants

10.3 Sample Size

We expect between 1000 and 2500 participants to enroll in this study. The final number is dependent upon both the final number enrolled in MTN-020, ASPIRE, and the proportion of ASPIRE participants who choose to enroll into MTN-025, HOPE. Power is discussed with the primary analyses as appropriate.

10.4 Participant Accrual, Follow-up and Retention

The majority of former ASPIRE participants are anticipated to enroll within the first 3-6 months after site activation, however this period could be shorter or longer depending upon accrual rates. Because of the potential to randomize to a monthly or a quarterly follow-up schedule, it is anticipated that the study will close to accrual 4 months ahead of the anticipated closure of the study. Based upon the timing of when a participant is enrolled, follow-up may last approximately 4-13 months.

10.5 Randomization

At the enrollment visit, participants will be randomly assigned to one of the two follow-up arms (monthly vs. quarterly) in a 1:1 ratio. The randomization scheme will be stratified by site and will be generated and maintained by the MTN SDMC. The randomized assignments will be in blocks to keep the balance of equal allocation. The SDMC will provide each study site with a series of numbered, sealed envelopes containing the randomization assignment for each participant. The envelopes will be assigned sequentially by site staff. The MTN SDMC will coordinate the randomization procedures, which will be specified in the SSP Manual. Assignment of the clinic randomization envelope is considered the effective act of participant randomization.

10.6 Blinding

This is an open-label and unblinded trial.

10.7 Data and Safety Monitoring Procedures

10.7.1 Study Monitoring Committee

In addition to the safety monitoring done by the PSRT (described in Section 8), the MTN SMC will be responsible for study oversight by conducting interim reviews of study progress, including rates of participant accrual, participant retention, protocol and intervention adherence, data quality, laboratory quality and completion of primary and secondary endpoint assessments. Since MTN-025 is not subject to DSMB review, the SMC also will review participant safety data, as specified in the MTN Manual of Procedures. These reviews will take place approximately every 6 months and as needed.

At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The SMC may consider recommending termination of this study if recruitment is lower than targeted, or if study data quality is poor. If at any time, a decision is made to discontinue participants, IPM, after consultation with the protocol team, will inform the US Food and Drug Administration (FDA). The Site PIs will notify the responsible ECs expeditiously.

10.7.2 Monitoring Quality of Study Conduct Operational Characteristics and Implementation

The study may be terminated or modified for poor accrual/recruitment, adherence/product use, and/or retention. Regular reports will be provided to the SMC that outline the potential impact on the study's ability to meet its objectives if there are deviations from the statistical design in terms of accrual/recruitment, adherence/product use, retention, and/or low HIV acquisition rate.

10.8 Primary Analyses

10.8.1 Primary Safety Analysis

Consistent with the primary safety objective, this analysis will characterize the safety profile for the overall population and the two arms. Because women in the monthly arm will be seen more frequently, we expect that more safety events will be recorded that would otherwise go unreported or unobserved with less frequent follow-up. Therefore, under this design a comparison between the arms is most appropriate for AEs that would be captured regardless of frequency of follow-up. These include the two key secondary outcomes of drug resistance and breakthrough infections. Those analyses will be covered in Section 10.9. As a supporting analysis, rates of AEs between the arms at quarterly visits will be compared, recognizing that this may be imperfect as well since monthly participants may have AEs resolved before a quarterly visit that may have remained unresolved were they on the quarterly schedule. Therefore, the AE rate in the monthly arm may look lower at quarterly visits because the AEs have been resolved.

Adverse events will be analyzed using MedDRA preferred terms. The number and percentage of participants experiencing each specific AE will be tabulated by severity and by relationship to treatment regimen. For the calculations in these tables, each participant's AE will be counted once under the maximum severity or the strongest recorded causal relationship to study product.

All AEs will be grouped by body system and a confidence interval for the incidence of each AE will be calculated overall and by arm. Finally, a listing of EAEs reported to the DAIDS Safety Office will provide details of the event including severity, relationship to study product, onset, duration and outcome.

Note that all of the above summaries will be calculated under the intention-to-treat (ITT) principle. However, participants off study product and/or those who are non-adherent that are included in these analyses could potentially lower the rate of safety and toxicity endpoints. Therefore, a 'per-protocol' analysis, where time off product is excluded from the analysis, will be used to explore the sensitivity of the conclusions obtained with the safety analysis under the ITT principle.

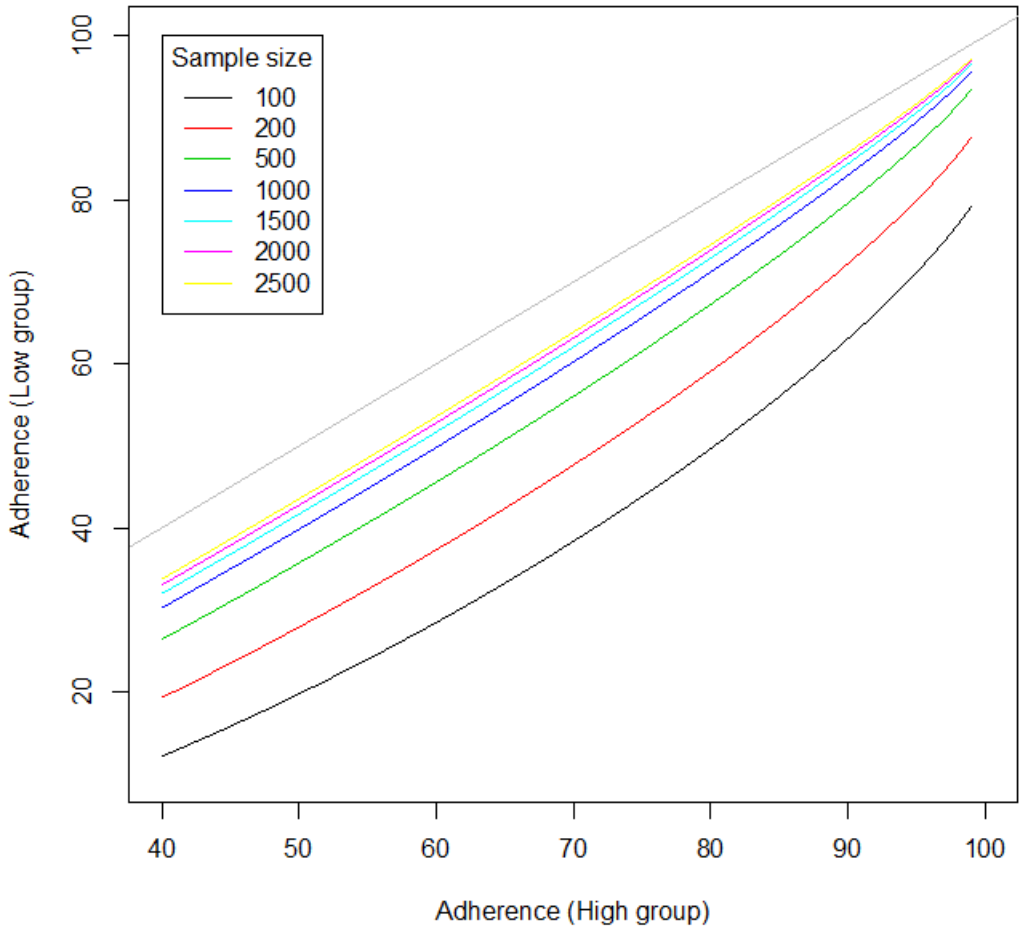
Assuming between 1000 and 2500 participants are enrolled with an average of 11 months of follow-up per participant, we expect between 917 and 2300 person-years of follow-up during this study. The assumed 11-month average follow-up reflects both loss to follow-up and staggered entry.

10.8.2 Primary Adherence Analysis

For the primary study aim related to adherence, participants will be categorized as adherent if drug is detected in all quarterly plasma samples when participants are not on a product hold. The arms will be compared using a chi-square test for 2x2 tables.

Based on this primary analysis plan, we calculated power under a variety of assumptions. The figure below shows hypothetical adherence rates for the two arms on the x- and y-axes. The curves connect the comparisons for which the comparison has 90% power. Each curve represents a hypothetical sample size across both arms ranging from 2500 (representing a potential full study analysis) to 100 (representing a potential within site or subgroup analysis). For example, with a sample size of 1500, if the higher adhering arm has 80% adherence, the study has 90% power to detect a difference between the two arms if the lower adherence arm has adherence of 73% or less. If the sample, size were instead 200, we could detect a difference between an 80% adherent arm and a 59% adherent arm.

Figure 2: Comparison of Rates of Adherence (Low Group Vs. High Group)



The analysis described above compares rates of perfect adherence as measured in plasma. In an effort to understand more complicated adherence patterns, secondary analyses for adherence will be performed. Similar analysis of residual drug levels in VRs will also be performed. Many of these will be informed by findings from ASPIRE and will be fully explained in a Statistical Analysis Plan prior to the completion of follow-up in MTN-025.

10.9 Analysis of Secondary Endpoints

Primary analysis of the two main secondary endpoints, HIV seroconversion and acquisition of ARV-resistant HIV infection will be conducted similarly. We will calculate the incidence overall and by arm for each endpoint. Use of new and additional HIV-1 prevention technologies, such as oral PrEP and/or topical vaginal gels, will be captured on standardized data forms and will be taken into account in the analysis of HIV-1 incidence. We will calculate confidence intervals for the differences between arms in incidence rates using the Poisson distribution. We anticipate this analysis to have low power since we will be comparing two arms in which participants are prescribed an active product that has been proven effective. Although, statistical summaries will be provided, the results will likely have to be judged based on clinical and public health

acceptability. Additional analyses will likely evolve based on results from ASPIRE. These will be outlined in the Statistical Analysis Plan prior to the end of study follow-up.

10.10 Missing Data

We are targeting a retention rate of 95% over the study period. Based on previous HIV Prevention Trials Network (HPTN) and MTN trials, we expect to have minimal missing data. In any situation with missing data, we will do appropriate secondary analyses that adjust for variables that may be related to the missingness mechanism. If missing data rates are higher than anticipated (over 10%), we will include covariates that are related to missingness in likelihood-based regression models. We will also perform sensitivity analyses to assess the potential impact of the missing data. These analyses will include imputing the data under the most extreme scenarios of information missingness, such as assuming everyone missing has an extreme value of the missing variable, and less informative imputation approaches.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study 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. Study CRF data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system.

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

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocpolicy.pdf) and the relevant appendix regarding source documentation (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocappndx.pdf).

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, for the investigational product tested, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval 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.

Audio files will be transcribed and immediately destroyed following a transcription quality assurance check. The site IoR or designee will be responsible for ensuring that these files have been destroyed.

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdfhttp://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdf).

12 CLINICAL SITE MONITORING

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

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

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

The IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of certain study procedures. The IoR/designee will also allow inspection of all study-related documentation by authorized representatives of the MTN LOC, SDMC, and LC; NIAID, FDA, IPM, OHRP and local and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Boards/Ethics Committees

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 will have obtained IRB/EC approval and the protocol will have been submitted to the FDA. The IoR will permit audits by the NIH, IPM, the FDA, OHRP, or any of their appointed agents.

13.2 Protocol Registration

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

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

Upon receiving final IRB/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 will be forwarded to DAIDS for cross-referencing with other INDs for the study product. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement executed by NIAID and IPM.

Study implementation will also be guided by a common study-specific procedures manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study product and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN LOC, SDMC, LC and other designated members of the Protocol Team.

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

13.4 Risk Benefit Statement

13.4.1 Risks

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

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

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

Participants at sites requiring partner notification in response to diagnosed STI or HIV infection could have problems in their relationships with their sexual partners. It is possible that the participant and her partner may feel the ring during sexual activity. Participants also could experience problems associated with use of study product in their partner relationships.

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

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

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

Please note: Study product risks will be updated when the safety and effectiveness data from ASPIRE are available.

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

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

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

13.4.2 Benefits

MTN-025 (HOPE) will only be implemented if the dapivirine vaginal ring as tested in MTN-020 (ASPIRE) is found to be safe and effective, therefore, participants in the HOPE study will experience the direct benefit of using a product that has been found to be safe and effective in preventing HIV acquisition and will be considered for potential regulatory approval. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help to understand issues important for broader implementation of the dapivirine ring and/or for the development of other safe and effective interventions to prevent HIV acquisition. Participants may also 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 will be provided STI treatment in accordance with WHO guidelines free of charge. In addition, STI testing, counseling and treatment, as well as HIV testing and counseling will be available for participants' partners. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals.

13.5 Informed Consent Process

Each study participant will provide written informed consent prior to both screening and enrollment. Written informed consent will also be obtained for long-term specimen storage and possible future testing, for off-site clinic visits as needed, as well as for participation in the 'Decliner Cohort'. Neither consent for long-term specimen storage nor off-site study visits are required for study participation. Further, participation in the 'Decliner Cohort' does not preclude MTN-025 full study participation. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://rsc.tech-res.com/policiesandregulations/). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

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

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

- Randomization and the importance of participants in both study groups to the success of the study
- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The real benefit of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time
- New information, including results of MTN-020 (ASPIRE)and IPM 027 (The Ring Study),and information about other effective HIV-prevention products will be provided to MTN-025 (HOPE) participants.

13.6 Participant Confidentiality

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

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored securely. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' identification numbers to identifying information will be stored in a locked file in an area with limited access. All digital audio files will be stored on password-protected computers. Audio files will be transcribed. Please see SSP for guidance regarding audio file destruction. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

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

13.7 Special Populations

13.7.1 Pregnant Women

Women who test positive for pregnancy at Screening or Enrollment Visits will not be eligible to participate in this study. Should a woman test positive for pregnancy after Enrollment, a product hold will be implemented but all follow-up visits will be completed and data collected per Section 7.6.2. A urine pregnancy test will be performed at scheduled study visits, and additionally at interim visits as indicated; the IoR/designee will temporarily discontinue study product for participants who test positive for pregnancy. During the informed consent process, women will be informed that the VR is not a method of contraception and the effects of the VR on a developing human fetus are unknown.

Animal studies have failed to demonstrate risk to the fetus, but there are no adequate and well-controlled studies in pregnant women completed to support their inclusion to date.

13.7.2 Children

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

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 and time away from work. Site-specific reimbursement amounts will be specified in the study informed consent forms. Each study site will determine appropriate compensation with their overseeing IRB/EC.

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 III. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will provide information regarding the known efficacy of the study product 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-Infected

Care for participants identified as HIV-infected is described in Section 9.6.

13.11 Study Discontinuation

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

14 PUBLICATION POLICY

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

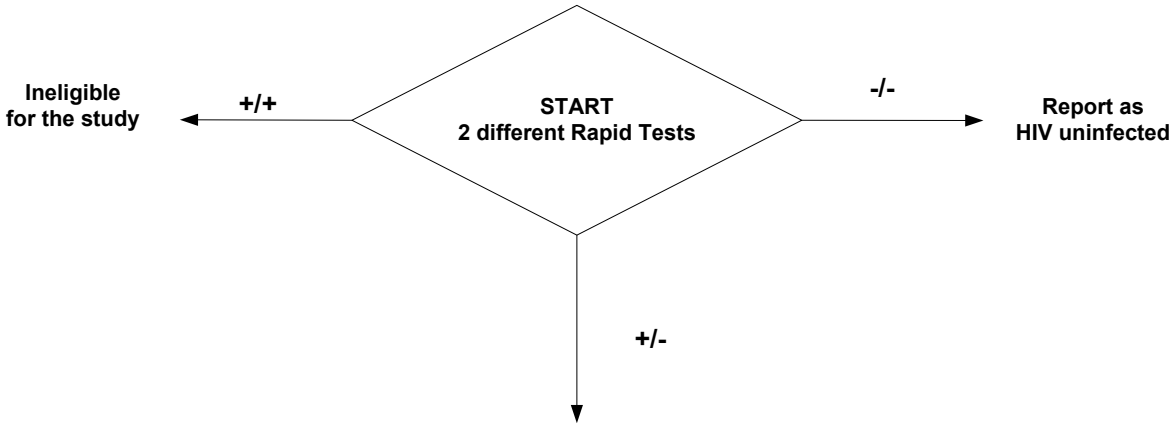
15 APPENDICES

Appendix I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

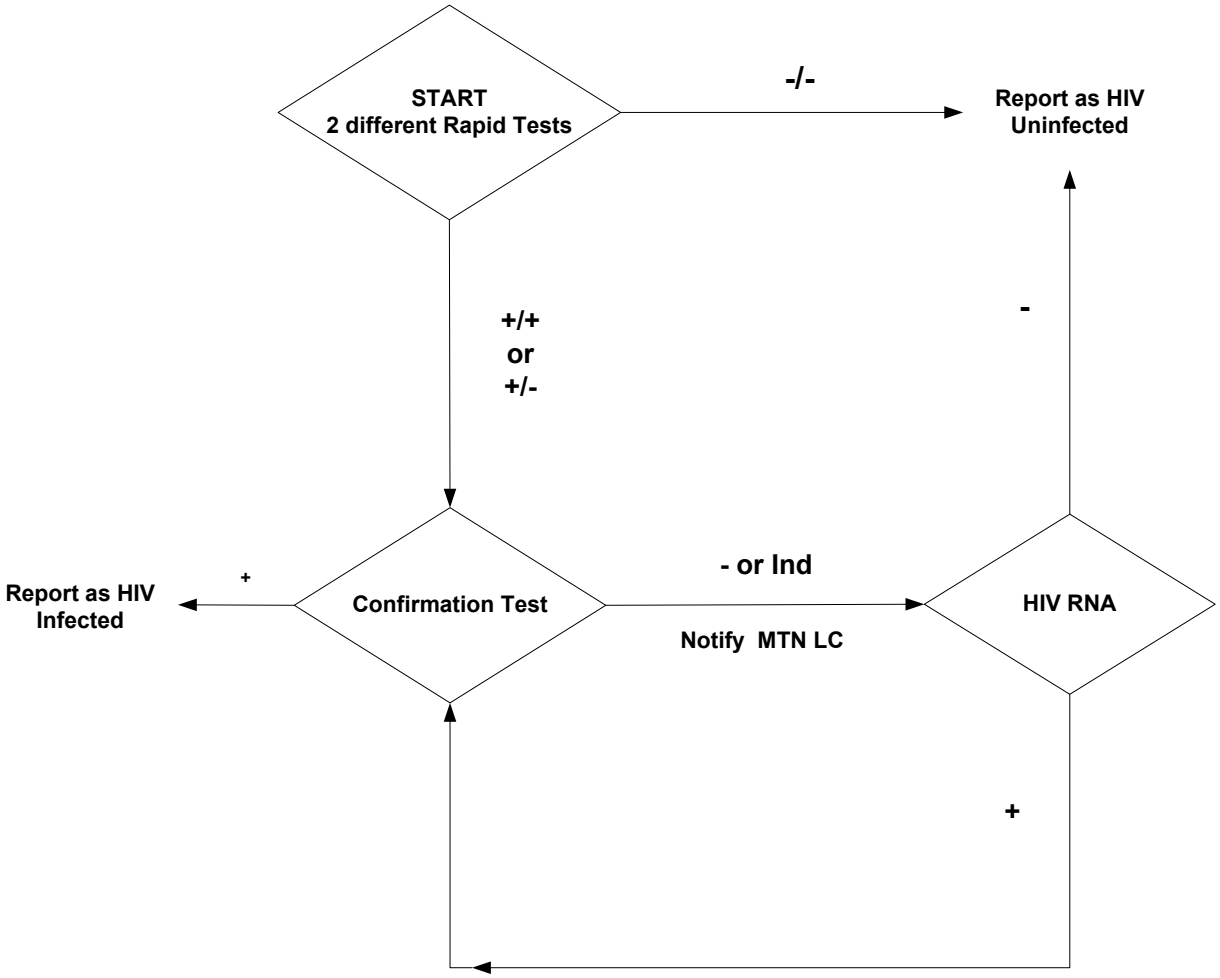
				Study Months			
		SCR	ENR	1, 2, 4, 5, 7, 8, 10, 11	3, 6, 9	PUEV ~12	Study Exit/ Term. Visit (~Month 13)
ADMINISTRATIVE AND REGULATORY							
Obtain informed consent		X	X				
Assign a unique Participant Identification (PTID) number		X					
Assess and/or confirm eligibility		X	X				
Collect/review/update locator information		X	X	X	X	X	X
Randomization			X				
Provide reimbursement for study visit		X	X	X	X	X	X
Schedule next visit		*	*	X	X	X	*
BEHAVIORAL							
Contraceptive counseling		X	X	X	X	X	*
HIV/STI risk reduction counseling		X	X	X	X	X	X
HIV pre- and post-test counseling		X	X	X	X	X	X
Protocol adherence			X	X	X		
Conduct a behavioral assessment			X		X	X	X
Conduct social harms assessment					X	X	
CLINICAL							
Obtain/update medical and menstrual history		X	X	X	X	X	X
Obtain/update concomitant medications		X	X	*	X	X	X
Conduct a physical examination		X	*	*	¥	X	*
Perform a pelvic examination		X	*	*	*	X	*
Offer contraceptives		*†	*	*†	*	*†	*†
Disclose available test results			X	X	X	X	X
Record/update AEs				X	X	X	X
Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings		*	*	*	*	*	*
LABORATORY							
URINE	hCG	X	X	X	X	X	X
	Urine culture	*†ǂ	*†ǂ	*†ǂ	*†ǂ	*†ǂ	*†ǂ
	NAAT for GC/CT	X	*†	*†	¥	X†	*†
BLOOD	HIV-1 serology	X	X	X	X	X	X
	CBC with platelets	X				X	
	Chemistries	X		*	*	X	
	Syphilis serology	X		*	*	X	
	Plasma		◊		X	X	X
PELVIC	Rapid test for Trichomonas	X	*†	*	¥	X	*
	Vaginal fluid (self-collected)		X	X	X	X	X
	Pap Smear interpretation	*					
	Adherence assessment(s): Returned Study VR			X	X	X	
STUDY PRODUCT/ SUPPLIES							
Offer condoms		X	X	X	X	X	X
Provision of study VR use instructions			X	*	*		
Provision of study VR			X	X	X		
Removal and collection of used/unused study VR				X	X	X	
Digital exam(s) by clinician to check VR placement			*	*	*		

*X mandatory, *If indicated, ᵀPer local standard of care, ¥ mandatory at month 6, if indicated at all other visits, ◊ for archive*

APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING-SCREENING/ENROLLMENT



APPENDIX III: ALGORITHM FOR HIV ANTIBODY TESTING FOR FOLLOW-UP



Ind: Indeterminate test results
LC: Laboratory Center

APPENDIX IV: SAMPLE INFORMED CONSENT DOCUMENT (SCREENING)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NICHD, NIMH, NIH

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

HIV Open-label Prevention Extension (HOPE)

Version 1.0
August 22, 2014

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

INFORMED CONSENT
This is a screening consent form. You are being asked to volunteer for screening tests to find out if you are eligible for a research study MTN-025, otherwise known as the **HIV Open-label Prevention Extension (HOPE)** trial. The research study you participated in, MTN-020: ASPIRE, *A Study to Prevent Infection with a Ring for Extended Use*, showed that the dapivirine vaginal ring can reduce the chances of HIV-uninfected women from getting the HIV virus by [SITES TO INSERT: from X to X percent]. The study also learned that the dapivirine vaginal ring is [SITES TO INSERT: *safe (meaning that they do not produce significant health problems in persons who take them)*] when used by HIV-uninfected women. Only through the participation of volunteers in clinical research can the safety and effectiveness of medicine be better understood. More data is needed on the safety of the dapivirine vaginal ring. Because you took part in the ASPIRE study, you are being offered the opportunity to use the safe and effective dapivirine vaginal ring as part of this new study. A total of 2629 women enrolled into MTN-020 (ASPIRE) and all former ASPIRE participants who are eligible for MTN-025 (HOPE) may take part. It is anticipated that approximately 1000 to 2500 former ASPIRE participants will enroll in HOPE.

This Microbicide Trials Network (MTN) study is funded by the US National Institutes of Health (NIH) and is being conducted across multiple countries across Africa. The International Partnership for Microbicides (IPM) supplies the study product.

[INSERT NAME OF PRINCIPAL INVESTIGATOR] is in charge of this study at this clinic. Before you decide if you want to screen for this study, we want you to learn more about the trial. Screening examinations and tests, which include interview questions, urine, and blood tests, a physical examination and an examinations of your vagina, will be performed to better understand your health. The study staff will explain the exams and tests to you and what is expected of you. Once you understand the screening tests, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

YOUR PARTICIPATION IS VOLUNTARY
It is important that you know the following:

- You are only being asked to have the screening tests at this time. Even if you agree to have the screening tests, you do not have to join this study.
- Your participation is voluntary; you do not have to have the screening tests if you do not want to participate in this study.
- You may decide not to have the screening tests, or to withdraw from the screening tests at any time, without losing your regular medical care.
- You will receive the results of the screening tests even if you are not eligible to join this study.
- Some people may not be able to join this study because of information found during the screening tests. You are asked to tell the study staff about any other studies you are taking part in, or thinking about taking part in. This is very important for your safety.
- If new information is learned about the study, or the study product, you will be told about this as soon as possible.

PURPOSE OF THE SCREENING TESTS AND THE STUDY
The main purpose of these screening exams and tests is to find out if you can join this research study. This research study will test if a vaginal ring containing the medicine dapivirine is used as directed and found to be safe in participants who attend clinic visits at different time points (monthly vs. every three months). Women will be in this study for approximately 13 months depending upon when they enroll in the study; however this period could be shorter or longer than anticipated.

STUDY PRODUCT
There is one kind of vaginal ring that will be used in this study, a ring containing dapivirine. Unlike ASPIRE, there is no placebo vaginal ring (a ring without the study medicine) in HOPE, so all HOPE participants will receive a vaginal ring containing dapivirine. This ring is the same dapivirine vaginal ring used in ASPIRE. Dapivirine vaginal rings have been previously tested and found to be generally safe, well-tolerated and effective in HIV prevention in women. HIV is the virus that causes AIDS. The medicines that are being tested by researchers to prevent HIV infection work in different ways. Dapivirine works by preventing HIV from making copies of itself, thereby stopping the spread of HIV in the body.

STUDY GROUPS
If you join MTN-025, you will be in one of two study groups. Both groups will use the same ring containing dapivirine, but the timing of clinic visits will differ. Half of the women will be in a study group that will be asked to come to the clinic for monthly visits. The other half of the women will come to the clinic for visits every three months. You will be assigned to a group by random chance, like flipping a coin. Neither you nor the staff can decide which follow-up schedule you will be assigned. Both of the study groups are important to this study.

WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN THE SCREENING EXAMS AND TESTS?
If you agree to have screening tests, they can be done today. Ideally, all procedures will be completed today. However if you have to come back to complete this visit, some procedures may need to be repeated.

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

- You will be asked questions about:
  - Where you live
  - Your medical health, what medications you are taking, and menstrual history
  - Other questions to ensure you are eligible for this study, and to make sure that you understand the study requirements.

- Study staff will:
  - Perform a physical examination
  - Talk with you about the requirements of the study including using an effective method of contraception throughout your participation in this study
  - Test your urine for:
    - Infections passed through sex
    - Pregnancy
      - If you are pregnant you cannot join this study because the risks to your baby are unknown.
      - If the study is still open after your pregnancy, you may come back here to find out if you are eligible.
      - If you are not pregnant, you will be told about ways to avoid becoming pregnant, such as the use of contraception.

  - Take a blood sample [Sites to insert amount]:
    - To test the health of your blood, liver and kidneys
    - To test for infections passed through sex, including HIV
      - You will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we know your results for sure. You must receive your HIV test results to be in this study. If the test shows you have HIV, you cannot join this study. We will tell you where you can get care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.

  - Perform a pelvic examination:
    - The study doctor or nurse will use a speculum, a plastic or metal instrument used to separate the walls of the vagina. The study doctor or nurse will look at your vagina and cervix for signs of infection, and other problems. Your cervix is located at the top of the vagina and it forms the lower end of the womb (uterus). They may also take some fluids to test for other possible problems if they feel it is necessary.
    - The study staff <u>may</u> also collect samples from your cervix for testing, including a "Pap test". If the test shows a problem, it could mean you should have more tests. If you have a written report confirming that you had a normal Pap test in the past 12 months or if you had an abnormal Pap test but had follow-up and a written report indicating no treatment was required, you will not need to have a Pap test during this visit.

- Give you treatment or refer you for treatment for infections passed through sex, if needed.
- Tell you about other services if you need them
- Offer you condoms. Condoms are highly effective in preventing the sexual transmission of HIV and reducing the risk for other sexually transmitted diseases (STDs). Study staff can provide you with condoms along with additional information about other ways to avoid getting HIV infection.
- Schedule your next visit to enroll in MTN-025, if you are eligible and willing

The study staff will review your test results with you when they are available. If the results show you can join the MTN-025 study, the study staff will explain the study to you and answer any questions you have. If you decide to be in this study, you will be asked to sign another consent form.

RISKS AND/OR DISCOMFORTS

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

Risks of 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 usually stops shortly after the examination.

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

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

BENEFITS

The primary benefit to joining this study is having access to a product that has been shown to be safe and effective in preventing HIV. If this screening visit shows you are eligible to participate, an enrollment visit will be scheduled.

You will have a physical examination, pelvic examination, and tests to check on the health of your blood, liver, and kidneys. If these tests show that you might have health problems, you will be told where to get medical care and other services available to you.

You will be counseled and tested for infections passed through sex. If you have these infections, you may be offered treatment for them, if needed. If you are infected with HIV, you will be told about medical care, counseling, and other available services that could be of help to you. For other health problems that cannot be treated at this clinic, the study staff will refer you

to other places where you may receive medical care. If your Pap test result shows anything that is not normal, you will be referred for advice and/or treatment.

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

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

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

COSTS TO YOU

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

REIMBURSEMENT

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

CONFIDENTIALITY

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

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH
- [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- IPM, the organization that supplies the study 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

[Sites to include/amend the following:] [LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed during sex to the *[LOCAL HEALTH AUTHORITY]*. Outreach workers from the *[HEALTH AUTHORITY]* may then contact you about informing your partners, since they also should be tested. If you do

not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the *[HEALTH AUTHORITY].*

The researchers will do everything they can to protect your privacy.

RESEARCH-RELATED INJURY
[Sites to modify with their site-specific research-related injury institutional policy:] It is unlikely that you will be injured as a result of having the screening tests. 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 or your insurance company will be charged for this treatment. You do not give up any legal rights by signing this consent form.

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

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

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

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

SIGNATURES

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

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

APPENDIX V: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NICHD, NIMH, NIH

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

HIV Open-label Prevention Extension (HOPE)

Version 1.0
August 22, 2014

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

INFORMED CONSENT
You are being asked to take part in the **MTN-025 HIV Open-label Prevention Extension (HOPE)** trial. The research study you participated in, MTN-020: ASPIRE, *A Study to Prevent Infection with a Ring for Extended Use*, showed that the dapivirine vaginal ring can reduce HIV-uninfected women's chances of getting the HIV virus by [SITES TO INSERT: from X to X percent]. The study also learned that the dapivirine vaginal ring is [SITES TO INSERT: *safe (meaning that it does not cause significant health problems)*] when used by HIV-uninfected women. More data is needed on the safety of the dapivirine vaginal ring. Because you took part in the ASPIRE study, you are being offered the opportunity to use the safe and effective dapivirine vaginal ring as part of this new study. A total of 2629 women enrolled into MTN-020 (ASPIRE) and all former ASPIRE participants who are eligible for MTN-025 (HOPE) may take part. It is anticipated that approximately 1000 to 2500 former ASPIRE participants will enroll in HOPE.

This Microbicide Trials Network (MTN) study is funded by the US National Institutes of Health (NIH) and is being conducted across multiple countries across Africa. The International Partnership for Microbicides (IPM) supplies the study product.

[INSERT NAME OF PRINCIPAL INVESTIGATOR] is in charge of this study at this clinic site.

YOUR PARTICIPATION IS VOLUNTARY
Before you decide if you want to join this study, we want you to learn about the study. The study staff will talk with you about the study and answer your questions. Once you read, discuss, and understand the study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep. You may decide not to join or to withdraw from the study at any time.

PURPOSE OF THE STUDY
This research study will test if a vaginal ring containing the medicine dapivirine is used as directed and found to be safe in participants who attend clinic visits at different time points

(monthly vs. every three months). Women will be in this study for approximately 13 months depending upon when they enroll in the study; however the duration of study participation could be shorter or longer than anticipated.

STUDY PRODUCT

There is one kind of vaginal ring that will be used in this study, a vaginal ring containing dapivirine. Unlike ASPIRE, there is no placebo vaginal ring (a ring without the study medicine) in HOPE, so all HOPE participants will receive a vaginal ring containing dapivirine. This ring is the same dapivirine vaginal ring used in ASPIRE. Dapivirine vaginal rings have been previously tested and found to be generally safe, well-tolerated and effective in HIV prevention in women. This study is testing whether a vaginal ring containing dapivirine can help to prevent the spread of HIV. HIV is the virus that causes AIDS. The medicine that is being tested to prevent HIV infection works in different ways. Dapivirine works by preventing HIV from making copies of itself, thereby stopping the spread of HIV in the body.

The staff can provide you additional information about other ways to avoid getting HIV infection. The most effective way to protect against getting HIV infection during sex is to use a condom every time you have sex.

STUDY GROUPS

If you join MTN-025, you will be randomly assigned (like flipping a coin) to one of two study groups. Both groups will use the same ring containing dapivirine, but the timing of clinic visits will differ. Half of the women will be in a study group that will be asked to come to the clinic for monthly visits. The other half of the women will come to the clinic for visits every three months. You will be assigned to a group by random chance, like flipping a coin. Neither you nor the staff can decide which follow-up schedule you will be assigned. Both of the study groups are important to this study.

WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN THE MTN-025 STUDY?

If you decide to enroll in the study, you will have a clinic visit today and monthly or every three months thereafter, depending upon which group you are randomly assigned to. You will insert a new vaginal ring monthly for approximately 12 months. For some participants, this period of time may be less, study staff will provide you with an estimate of how long you will use the ring. You will have a final study visit to check on your health approximately 4 weeks after the final ring is removed. Study visits may be required beyond the final study visit to monitor your health. Visits will take approximately *[site to insert required length of time].*

You will be asked to:

- Confirm you are able to join the study and that you understand the study requirements
- Answer questions about your vaginal practices, including sexual activity
- Provide updated information about where you live and how we can contact you
- Describe any changes in your health, what medicines you are taking, and your menstrual periods
- Describe any health problems you have had since your last visit, including problems with the study ring

You will be asked to use a study vaginal ring. As part of using this ring you will:

- Talk with study staff about how to properly wear and use the study ring

- Receive new study rings (monthly or every three months) and insert a new study ring (monthly). If you are inserting a new ring at a clinic visit, and you are having difficulty a study clinician may help you
- If needed, have an examination performed to ensure the ring is properly inserted.
- Return your vaginal ring(s) to study staff. Study researchers will keep these rings and run additional tests on them. These tests will help researchers better understand your ring use.
- Be able to return to the clinic to have the ring reinserted if the ring falls out and you are uncomfortable reinserting it yourself

You will be asked to answer questions about:

- Your experience using the vaginal ring, including whether or not the ring was removed from or fell out of your vagina.
- Any problems you may have had during your participation in this study.
- Vaginal practices that may affect how the study drug is absorbed by your body.
- Things that may make you uncomfortable, such as questions about drug use. You may use a computer to answer these questions or a staff member may ask you these questions. It is important that you know that you will answer these questions in private and your responses will be kept confidential.

You will have the following clinical procedures performed:

- A physical examination
- Provide a sample of blood [insert amount] to:
    - Check the health of your blood, liver and kidneys
    - Test for HIV. You will be told your HIV test results as soon as they are available. 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 clearly positive, but also not clearly negative. In that case, we will do more tests until we know your results for sure. You must receive your HIV test results to be in the study. If the test shows you have HIV, you cannot join the study. We will 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.
    - Additional testing may be performed as part of quality control.
    - See how much of the study product is being absorbed by your body and how it affects your body.
- Provide a urine sample to:
    - Check to see if you are pregnant
    - Test for infections passed through sex
- Provide vaginal fluid and cervical fluid samples:
    - To see how the dapivirine vaginal ring protects against HIV and to explore the health of the female genital tract. The vaginal fluid and cervical fluid collected will be used for research purposes only.
- A pelvic examination when the vaginal ring is removed for the final time. The study doctor or nurse will use a speculum. A speculum is a plastic or metal instrument used to

separate the walls of the vagina. It is used so the doctor or nurse can examine the vagina and the cervix during the examination. Your cervix is located at the top of the vagina and it forms the lower end of the womb (uterus). They will check for signs of infection, and other problems. They may also take some fluids to test for STIs and other possible problems if they feel it is necessary

As part of the clinical procedures you will:

- Receive the results of your tests when available
- Learn about other services available to you
- Receive treatment or be referred for treatment for problems that the study staff may find.
- Receive counseling. You will discuss:
    - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to prevent HIV and other infections passed through sex
    - The rules of the study and how to follow the rules
    - Contraception and ways to prevent getting pregnant
- Be offered condoms. Condoms are highly effective in preventing the sexual transmission of HIV and reducing the risk of other sexually transmitted diseases (STDs). Study staff can provide you with condoms along with additional information about other ways to avoid getting HIV infection.
- You will schedule your next visit

If you leave the study early, you will be asked to complete a final clinic visit and evaluations. Various procedures will be completed at this visit, including a pregnancy and HIV test.

It may be necessary for additional visit(s) and procedures in the event of unforeseen or unanticipated results; difficulties in sample shipping, processing, or testing; and/or if you are experiencing any symptoms or changes in your physical condition. For example, at any time during the study, vaginal and/or cervical swabs, blood samples and urine may need to be collected if you are having symptoms or if you are suspected to have an infection.

Interim/Unscheduled Visits

Study staff will discuss with you the importance of contacting the clinic as soon as you notice changes in your physical condition or when you experience health related issues. It may be necessary to come to the clinic for an unscheduled visit. Also, it is possible that you may be asked to come to the clinic for an unscheduled visit in the event of an abnormal test result; difficulties in sample shipping, processing, or testing; or for other reasons.

In-depth Interview(s) and Group Discussions

You may be asked to participate in interview(s) with a trained staff member or you may be asked to participate in a group discussion with other study participants about opinions that you or other participants have. If you are asked to participate in these study activities, you will be compensated for your time and effort.

If you are asked to participate in a group discussion, you will be asked to discuss your use of the study product, your feelings about the study product and trial participation, your vaginal

practices and other questions that can help researchers to better understand participants' experiences while taking part in the study. These discussions will last about one hour.

If you are asked to participate in an interview, you will be asked questions about your use of the ring, your preferences and opinions, your experiences with using the ring during sex, and any problems you may have had using the ring. The interviews will be audio-recorded to make sure to record your words exactly how you said them. The voice recordings will be destroyed as soon as the audio recording has been typed and checked. The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or fake names. This means that no one other than the MTN-025 (HOPE) study team will have access to your responses. The information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-025(HOPE) study team for the purposes of this research.

If you become infected with HIV
Your participation in this study will not cause HIV infection. However, there is always a chance that through sexual activity or other activities you may become HIV-positive. If the HIV tests confirm that you have been infected with HIV, you will stop using the ring, but we will ask you to continue to come into the clinic for regularly scheduled visits for some of the study procedures. You will have more blood tests at different time points after your HIV infection is discovered to find out which drugs would be inappropriate for your type of HIV-1 (HIV drug resistance), the amount of immune protection in your blood (CD4+ T-cell count), and the amount of HIV in your blood (viral load). You may be referred to other research studies. If you join another study it may not be necessary to collect additional blood for testing. In the event you become HIV-positive, study staff will counsel and refer you for medical care and other available services while you are in this study.

It may be necessary, depending upon local and national health requirements, for study staff to report diseases, including HIV, identified among MTN-020 (ASPIRE) study participants. The reportable diseases at this site are [Sites to insert].

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 examination.

Risks of Study Rings
The study rings can cause some side effects, such as an allergic reaction. Signs of an allergic reaction include, but are not limited to: Rash or other skin irritation, itching, joint pain, or difficulty in breathing. We do not yet know all the side effects of the rings. Some, but not all women who used the 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. 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 symptoms associated with toxic shock syndrome, i.e., sudden high fever, a faint feeling, diarrhea, headache, a rash, and muscle aches.

Finally, it is also possible that you or your partner may feel the ring during sexual activity. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

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

- Vaginal bleeding
- Headache
- Fatigue
- Itching on the external parts of your genitals
- Abdominal discomfort
- Abdominal pain
- The loss of bladder control
- Nausea
- Vaginal or genital discharge

Other Possible Risks
If you become infected with HIV and continue to use the ring it is possible that you may develop HIV drug resistance. This means that any virus that is drug resistant will survive and continue to reproduce (make copies of new HIV) in the presence of the drug that normally weakens or kills it. HIV drug resistance could make it difficult to use dapivirine or drugs like it to treat the HIV. Drug resistance only occurs if you were to become infected with HIV and continue to use the study product.

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

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

If you are chosen to participate in the group discussion, other participants will hear what you say. We will not reveal your full name to other participants. We will also ask every participant

not to tell anyone outside of the group what any person said during the discussion. While it is not at all likely that your discussion will be made public, we cannot guarantee that everyone will keep the discussion private.

BENEFITS

[SITES TO UPDATE: Participants in the MTN-025 (HOPE) trial will experience the direct benefit of using a vaginal ring that has been found to be safe and efficacious in preventing HIV transmission.]

In addition, you will have physical examinations, pelvic examinations, and tests to check on the health of your blood, liver, and kidneys. If these tests show that you might have health problems, you will be told where to get medical care and other services available to you.

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

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

PREGNANCY AND BREASTFEEDING

The dapivirine ring is not birth control. You must agree to use an effective method of birth control such as an intrauterine contraceptive device (IUCD), birth control pills or other hormonal-based method (except for vaginal rings), unless you underwent a medical procedure to permanently be unable to become pregnant, i.e., sterilization.

We do not know if the dapivirine ring has any effect on pregnancy, on the fetuses of a women who use the vaginal ring while pregnant, or on the babies of women who use the ring while breastfeeding. Because of this, pregnant and breastfeeding women may not join this study. You may be able to start using the vaginal ring after your pregnancy, provided that you are not breastfeeding. The study staff will talk more with you about this after your pregnancy. Women who join the study must agree to use effective contraception 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 or your baby may need. The study does not pay for this care. You will stop using the ring, but we may ask you to keep coming here for study visits as originally planned. We will change the study procedures as needed to protect your health while you are pregnant. *[Sites to include/amend the following:* We may also contact you to find out about the health of your pregnancy, and the health of your baby up to one year old, if you have a baby. We may also contact you about a study that collects information about pregnancy and babies up to one year old.] The outcome of your pregnancy is important to study staff; therefore your pregnancy will be followed until the results of your pregnancy are known.

NEW INFORMATION

You will be told about new information from this or other studies that may affect your welfare or willingness to stay in this study. It is important you know that the study product, the dapivirine

ring, is among the most advanced HIV prevention products that can be offered to you [SITES TO INSERT MTN-020 DATA HERE]. In addition to being tested as part of the ASPIRE trial, the ring was also tested in IPM 027 [INSERT IPM 027 DESCRIPTION AND RESULTS AND/OR UPDATE, IF AVAILABLE, HERE]. In the future, vaginal rings containing more than one type of medicine may become available. If a new product like this were to become available, it could be more protective than the ring tested as part of MTN-020 (ASPIRE) and IPM 027 (The Ring Study), leading to fewer HIV infections, however, no other vaginal ring has been found to work at this time.

It is also important for you to know that other drugs are being tested for HIV prevention. The HIV prevention researchers working on this MTN-025 (HOPE) are committed to sharing any data with you that becomes available, regardless of the product, if it is found to be effective in preventing the transmission of HIV. You will also be told when study results may be available, and how to learn about them.

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

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

- The study is cancelled by the US FDA, US NIH, International Partnership for Microbicides, the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/ the Ethics Committee (EC). An IRB/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
- A study doctor decides that using the vaginal ring would be harmful to you
- You require a treatment that you may not take while using the study vaginal ring
- You have a bad reaction to the study vaginal ring

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

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

ALTERNATIVES TO PARTICIPATION
[*Sites to include/amend the following:]* There are no gels, tablets or vaginal rings currently available in this country to protect against HIV during sex. Consistent use of condoms is the only available known way to protect against HIV during sex. 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 contraception. 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 may receive [*Sites to insert amount $xx*] for any visits which occur in between your normally scheduled visits.

CONFIDENTIALITY
Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff may use your personal information to verify that you are not in any other research studies. [Sites to insert information about systems currently in place to ensure participants are not part of other conflicting studies, including biometric identification systems.] 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
- [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- IPM, the organization that supplies the study 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

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

The researchers will do everything they can to protect your privacy.

RESEARCH-RELATED INJURY

[Sites to modify with their site-specific research-related injury 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 or your insurance company will be charged for this treatment. You do not give up any legal rights by signing this consent form.

CLINICALTRIALS.GOV

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

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

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

PROBLEMS OR QUESTIONS

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

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

SIGNATURES

[Sites to insert signature/initial blocks as required by the local IRB/EC:]

[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

There might be a small amount of blood, vaginal fluid and cervical fluid samples left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your leftover blood, vaginal fluid, and cervical fluid samples, and related health information for use in future studies. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range. If you agree, your samples and related health data will be stored safely and securely at facilities that are designed so that only approved researchers will have access to the samples. Some of these research facilities may be outside of your country. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. You can still enroll in this study if you decide not to have leftover blood, vaginal fluid and cervical fluid samples stored for future studies. If you do not want the left-over blood, vaginal fluid and cervical fluid samples stored, we will destroy these left over specimens. Any future studies that may be done will also have to be approved by an Ethics Committee/ Institutional Review Board. 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.

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

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

CONSENT FOR OFF-SITE VISITS

[Sites to modify as needed]

Members of the research team at this clinic may be able to schedule off site visits with you at your home or at another location as part of the study. If needed, and, if you agree, some of the scheduled study visits and some of the study procedures may take place at your home or other location outside of the research clinic, if you are unable to come into the clinic. If, for example, you need to receive a new ring or to have a urine or blood sample collected, study staff could come to you your home or meet you at another location, if you give your permission and if the study staff determine that it is appropriate. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the time it will take) and the procedures in-place to maintain your information in a confidential manner. However it is important that you know that off-site visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

In order to conduct visits outside of the clinic, we will need you to give us permission to do so. Please read carefully the following statement and initial and date one option. Choosing not to be visited outside of the study clinic will not affect your participation in this study. Even if you agree today, you can withdraw your consent for off-site visits at any time by providing your request in writing to the person in charge of this study. In addition, before each off-site visit, we will confirm with you that you still agree and remember today's discussion.

_____ I DO agree to be visited at a location other than the study clinic by clinic staff, when necessary

Initials and Date

_____ I DO NOT agree to be visited at a location other than the study clinic by clinic staff, when necessary

Initials and Date

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to participate in this study, please sign your name or make your mark below.

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

APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT (MTN-025 DECLINER GROUP)
MTN-025

SAMPLE INFORMED CONSENT FORM-
Screening and Enrollment MTN-025 Decliner Group

DIVISION OF AIDS, NIAID, NIH, NIMH, NICHD

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

Version 1.0
August 22, 2014

PRINCIPAL INVESTIGATOR:
PHONE:

INFORMED CONSENT
You are being asked to take part in this research study because you are a woman who took part in the MTN-020 (ASPIRE) trial and have decided to delay, decline to take part in the MTN-025 (HOPE) trial. Other women like you will participate in this study across multiple sites. Before you decide if you want to join this study, we want you to know about the study. This Screening/Enrollment consent form gives you information about this study. MTN-025 (HOPE) staff will talk with you about the study and answer any questions you may have.

This Microbicide Trials Network (MTN) study is funded by the US National Institutes of Health (NIH) and is being conducted across multiple countries across Africa. A total of 2629 women enrolled into MTN-020: ASPIRE and all former participants who are eligible may take part in the MTN-025 or in the MTN-025: Decliner Group.

YOUR PARTICIPATION IS VOLUNTARY
Participation in this study is voluntary. You will be asked to sign or make your mark on this form to indicate whether you agree to participate in this study. Before you decide whether to be in MTN-025 Decliner Group, we would like to explain the purpose of the study. If you decide to enroll in this study, you may decide to withdraw from the study at any time. There will be no penalty for refusing to participate or choosing to withdraw from this study.

It is important that you know that if you change your mind and wish to take part in the MTN-025 trial, you can enroll, provided that the study is ongoing and that you are eligible.

PURPOSE OF THE DECLINER GROUP
The main goal of the Decliner Group is to better understand MTN-020 (ASPIRE) participants' reasons for refusal to take part in the MTN-025 (HOPE) trial. MTN-025, is a study that provides former ASPIRE participants with access to the dapivirine vaginal ring, a product that has been shown to reduce the chances of women from getting the HIV virus by [To be updated: X to X percent]. The study also learned that the dapivirine vaginal ring is [To be updated: *safe (meaning that it does not produce significant health problems in persons who take it)*].

STUDY PROCEDURES
It is expected that the procedures involved with the MTN-025 Decliner Group will be completed in one visit. If you agree to join this study, you will be asked to answer questions about your behavior(s) and you also may be asked to complete an in-depth interview (IDI) in the presence of one or two MTN-025 (HOPE) research staff members. If you agree to take part in this study, the interviewer will ask you some brief questions and write your responses on a form. Multiple visits may be needed to complete the IDI and questionnaire(s). During the IDI, the interviewer will also ask in-depth questions, during which time notes may be taken and the conversation will be audio-recorded.

You will be asked some general questions, such as your age, education, living situation, relationship status and health. You will also be asked about other clinical trials or HIV-related studies that you may be currently participating in. The interviewer will also ask questions about your experiences while participating in the ASPIRE trial. These will include questions about different ways women used their study product, their sexual practices, as well as your use of the study product and your sexual practices.

We expect the interview will take approximately 2 hours. The IDI it will be completed at a place agreed upon by you and the study staff, which may be your home, a designated neutral study interview location, the clinic you went to for your ASPIRE visits or another convenient place of your choice.

The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or fake names. The information that links you to the research data will be kept in a secure location that will be accessed only by members of the HOPE study team for the purposes of this research.

To obtain information about your participation in ASPIRE, the HOPE study team may need to access your ASPIRE research records. By signing this form, you are giving the HOPE study team permission to look up and record the needed information from your research record.

RISKS AND/OR DISCOMFORTS
During the interview we may ask you some questions that cause you to feel embarrassed or uncomfortable. You can choose not to answer questions in the interview at any time. It is also possible that people or family members may find out you are participating in this study. As a result, they may ask questions about the study, treat you unfairly, or you may encounter problems in being accepted by your family and/or community.

Another possible risk of this study is loss of confidentiality of the information you give. Every effort will be made to protect your confidential information, but this cannot be guaranteed. To reduce this risk, we will strictly protect the information recorded during your interview. The audio recording, notes, and analyses from these materials will be kept confidential. This means that no one other than the HOPE interview team will have access to your responses. The information that links you to the research materials will be kept in a secure location. Your audio recordings will also be kept in a secure location and only people involved with the study will have access to these recordings. When the information on the audio recording is typed onto paper and fully checked, the recording will be destroyed. Study leaders will make sure this happens.

[Sites to modify based upon their institutional policy: In the unlikely event that you get injured as a result of your study participation, it is important that you know the US National Institutes of Health (NIH) does not have a mechanism to provide direct compensation for research-related injury.]

NEW INFORMATION
You will be told about new information from this or other studies that may affect your welfare or willingness to stay in this study.

BENEFITS
There are no direct benefits to participating in this study. However, the information you provide may help researchers improve the design of future studies.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT
You may be removed from this study without your consent for the following reasons:

- The study is stopped or canceled
- The study staff feels that staying in the study would be harmful to you
- The study is stopped by NIH, the MTN, International Partnership for Microbicides (IPM), the Office for Human Research Protections (OHRP), other government or regulatory authorities, or site IRBs/ECs
- Other administrative reasons

ALTERNATIVES TO PARTICIPATION
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 we know about.

COSTS TO YOU
There is no cost to you for being in this study.

REIMBURSEMENT
[*Sites to modify/insert text as necessary for planned local reimbursement:*]
You will receive [$xx] for your time, effort, and travel.

CONFIDENTIALITY
We will do our best to make sure that the personal information gathered for this study is kept private. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

This Microbicide Trials Network (MTN) study is funded by the US NIH.

Your records may be reviewed by any or all of the following:

- The MTN-025 study staff
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- Site IRBs/ECs
- IPM

- Representatives of the US Federal Government, including the US FDA, US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH

PROBLEMS OR QUESTIONS
If you ever have any questions about this study, 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 telephone number and/or physical address of above].

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

[Sites to modify with their site-specific research-related injury based upon their institutional policy:
RESEARCH-RELATED INJURY
It is unlikely that you will be injured as a result of taking part in the MTN-025 Decliner Group. 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 or your insurance company will be charged for this treatment. You do not give up any legal rights by signing this consent form. *]*

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

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

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MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

Microbicide Trials Network

Funding Agencies:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
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US National Institute of Mental Health
US National Institutes of Health

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IND Sponsor:
International Partnership for Microbicides

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Protocol Chair:
Jared Baeten, MD, PhD

Protocol Co-chairs:
Nyaradzo M. Mgodi, MBChB, MMed
Thesla Palanee-Phillips, PhD

Version 2.0

December 16, 2014

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

TABLE OF CONTENTS

Table of Figures

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	Antiretroviral
AST	aspartate aminotransferase
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
AUC	area under plasma concentration-time curve
AVAC	Global Advocacy for HIV Prevention
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
CAB	community advisory board
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CBC	complete blood count
CDC	U.S. Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
Cmax	maximum concentrations
Cmin	minimum concentrations
CMRB	Clinical Microbicide Research Branch
CRF	Case Report Form
CROI	Conference on Retroviruses and Opportunistic Infections
CT	Chlamydia trachomatis
CTA	clinical trial agreement
CTU	Clinical trials unit
CWG	Community Working Group
DAERS	DAIDS Adverse Events Reporting System
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAPY	di-aminopyrimidine
DLV	Delavirdine
DNA	deoxyribonucleic acid
EAE	expedited adverse event
EC	Ethics Committee
EC_{50}	50% effective concentration
EFV	efavirenz
FDA	Food & Drug Administration (U.S.)
FHCRC	Fred Hutchinson Cancer Research Center
FTP	File Transfer Protocol
g	Grams
GC	*Neisseria gonorrhoeae*

GCP	Good Clinical Practice
GMP	good manufacturing practices
hCG	human chorionic gonadotropin
HOPE	HIV Open-label Prevention Extension
hu-PBL	human peripheral blood lymphocytes
hu-SCID	human severe combined immunodeficient
HIV-1	human immunodeficiency virus-1
HPTN	HIV Prevention Trials Network
IATA	International Association of Air Transport
IB	Investigator's Brochure
ICF	Informed Consent Form
IDI	in-depth interview
IND	Investigational New Drug
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
ITT	intent-to-treat
IUCD	intrauterine contraceptive device
JHU	Johns Hopkins University
JKUAT	Jomo Kenyatta University of Agriculture and Technology
KOH	potassium hydroxide
LC	Laboratory Center
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantification
LOC	Leadership and Coordinating Center
µg	microgram
µM	micromolar (10^{-3} mol/m^3)
mg	Milligram
mL	Milliliter
MO	Medical Officer
MOP	Manual of Operational Procedures
MTN	Microbicide Trials Network
MU	Makerere University
MU-JHU	Makerere University - Johns Hopkins University
NAAT	nucleic acid amplification test
ng	nanogram per milliliter
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
nM	nanomolar (10^{-6} mol/m^3)
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
PCR	polymerase chain reaction

PEP	post-exposure prophylaxis
pg/mL	picogram/milliliter
PID	pelvic inflammatory disease
PK	Pharmacokinetic
PPD	Pharmaceutical Product Development, Inc.
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PSP	Prevention Sciences Program
PSRT	Protocol Safety Review Team
PTID	participant identification
PUEV	Product Use End Visit
QD	quaque die (once daily)
RNA	ribonucleic acid
RPR	rapid plasma reagin
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SSP	study specific procedure(s)
STI	sexually transmitted infection
TEAE	treatment emergent adverse event
UCSF	University of California- San Francisco
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNC	University of North Carolina
UPMC	University of Pittsburgh Medical Center
USA	United States of America
UTI	urinary tract infection
VR	vaginal ring
WHO	World Health Organization
wt	wild-type

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women
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MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

INVESTIGATOR SIGNATURE FORM

Version 2.0

December 16, 2014

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-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

PROTOCOL SUMMARY

Short Title:	HIV Open-label Prevention Extension (HOPE)
IND Sponsor:	International Partnership for Microbicides
Funders:	Division of AIDS, NIAID, NIMH, NICHD, US NIH
Protocol Chair:	Jared Baeten, MD, PhD
Protocol Co-chairs:	Nyaradzo M. Mgodi, MBChB, MMed Thesla Palanee-Phillips, PhD
Sample Size:	Eligible former MTN-020 participants
Study Population:	Former MTN-020 participants who are HIV-uninfected and not pregnant *Decliner Population: Former MTN-020 participants who decline participation in the main MTN-025 study and meet eligibility criteria as described in Sections 5.4 and 5.5*
Study Sites:	Approved former MTN-020 sites
Study Design:	Phase 3B, open-label, multi-site trial Following demonstration of safety and efficacy of the dapivirine vaginal ring in MTN-020, eligible MTN-020 participants will be offered enrollment into MTN-025, a trial designed to obtain additional safety and adherence data in women.
Study Duration:	Approximately 13 months of follow-up per participant with a projected accrual period of approximately 6 months at each site. *Note: In an effort to provide women with the maximum ability to enter the MTN-025 trial, following the formal ~6-month study accrual period participants will continue to be enrolled throughout the duration of the trial, provided that at least 4 months of time on study is supported by the timeline. An adjusted (shortened) follow-up period will be employed for women who enroll after the formal accrual period.*

Follow-up may be extended beyond 13 months based on need and requirements and with the necessary approvals.

Study Product: Dapivirine VR

Study Regimen: Participants will receive a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine to be replaced each month for a total period of 12 months of use.

The study follow-up schedule will be monthly for the first three months, then quarterly thereafter (Figure 1), reflecting a transition to a more real-world type of follow-up (versus a clinical trial approach) that would be important for informing implementation.

Figure 1: Sample Study Visit Schedule

Primary Objectives:

1. Safety
   - To characterize the safety profile associated with the open label use of the dapivirine vaginal matrix ring (25 mg) in women

2. Study Product Adherence
   - To characterize adherence to the open label use of the dapivirine vaginal matrix ring (25 mg) in women

Primary Endpoints:

1. Safety
   - Grade 2 adverse events (AEs) judged to be related to the dapivirine vaginal ring
   - Grade 3 and higher AEs
   - All serious AEs

2. Study Product Adherence
   - Residual levels of dapivirine in returned vaginal rings
   - Blood dapivirine levels

Secondary Objectives:

1. Incidence
   - To assess incidence of HIV-1 infection

2. Drug Resistance
   - To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection

Secondary Endpoints:

1. Incidence
   - HIV-1 infection as measured by the protocol algorithm

2. Drug Resistance
   - HIV-1 drug resistance mutations among participants who acquire HIV-1, as measured by standard genotype analysis and more sensitive methods to detect low frequency drug-resistant variants

Exploratory Objectives:

1. To explore participant understanding of efficacy

2. To explore ring acceptability in the context of known efficacy

3. To assess the feasibility of a quarterly follow-up visit schedule

4. To describe the genital microenvironment in women exposed to the dapivirine vaginal ring

5. To characterize the MTN-020 participants who choose not to enroll into MTN-025

Exploratory Endpoints:

1. Understanding of efficacy
   - Self-reported understanding of partial efficacy

2. Understanding of ring acceptability in the context of known efficacy
   - Self-reported product acceptability and attitudes towards combination prevention

3. Feasibility:

- Participant report of product storage issues and feasibility regarding the follow-up schedule
- Visit retention
- Proportion of returned rings (used and unused)

4. Genital microenvironment
   - In genital swab samples, candidate biomarkers of safety, adherence and efficacy, HIV exposure and antiretroviral resistance, and genital microflora

5. Characterization of MTN-020 participants who do not enroll in MTN-025
   - Participant report of the factors that led to her decision to decline enrollment into MTN-025

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women
Protocol Number:	MTN-025
Short Title:	HIV Open-label Prevention Extension (HOPE)
Date:	December 16, 2014

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2 INTRODUCTION

2.1 Microbicides and Human Immunodeficiency Virus (HIV) Prevention

In 2012, 2.3 million people became newly infected with HIV and 1.6 million lost their lives to acquired immunodeficiency syndrome (AIDS). Every 60 seconds, a young woman is infected with HIV.[1] According to the Joint United Nations Programme on Human Immunodeficiency Virus (HIV)/AIDS (UNAIDS) Global Report, the estimated number of individuals living with HIV is 35.3 million globally. Given the high rates of HIV infection among women, female controlled prevention options remain a global priority. Women and girls continue to be affected disproportionately by HIV in sub-Saharan Africa, where women account for approximately 60% of people living with HIV. The ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.

Unprotected heterosexual intercourse is currently the leading mode of HIV acquisition among women. Correct and consistent use of latex condoms is one proven method of preventing HIV acquisition; however, condoms are widely regarded as inadequate prevention options for women, because many women are unable to negotiate condom use with their partners. The most widely available HIV prevention methods require the consent of the male partner. Thus, developing HIV prevention options that women can use remains a global concern. Vaginal microbicides, which are self-initiated and controlled, offer women a critically needed biomedical prevention tool that will complement existing HIV prevention strategies as well as future products being developed.

With successful proof-of-concept that antiretroviral (ARV)-based microbicides reduce the risk of HIV-1 acquisition, confirmatory work and further trials involving different ARV compounds, various formulations, and different dosing strategies, are required to provide options to end users and to improve upon the level of product effectiveness.

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

Multiple clinical trials have evaluated the safety of dapivirine in VRs, gels and in an oral formulation. These clinical trials support the favorable safety profile and tolerability of dapivirine in general and specifically in vaginal delivery formulations. Initiation of the MTN-025 study of the dapivirine VR will be contingent upon demonstration of the safety and efficacy of the product in the ongoing MTN-020 (ASPIRE) study. The specific level

of effectiveness required to trigger activation of the MTN-025 study will be decided upon following discussions with key stakeholders including regulatory authorities, community representatives, and sponsoring agencies.

2.2 Dapivirine Vaginal Ring (VR)

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.[2] The dapivirine matrix VR is a flexible ring containing 25 mg of drug substance dispersed in a platinum-catalyzed cured silicone matrix. When delivered via VR, dapivirine has demonstrated favorable safety and pharmacokinetic profiles as described below.

Dapivirine was originally developed by Janssen Research and Development (formerly Tibotec Pharmaceuticals Ltd.), a subsidiary of Johnson & Johnson, as an oral ARV compound for treatment of HIV/AIDS and was tested in Phase 1 and 2 clinical trials in more than 200 participants.[3] However, dapivirine is also a promising topical microbicide candidate due to its proven *in vitro* and *in vivo* efficacy and favorable safety profile as well as its physical and chemical properties. Dapivirine has potent activity against wild-type HIV-1 strains and strains harboring different resistance-inducing mutations. Dapivirine's ARV profile is superior to that of several other NNRTI drugs, including nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). Like other NNRTIs, *in vitro* tests have also shown that dapivirine is not active against HIV-2 and has little or no activity against common sexually transmitted infections (STI), therefore, it is not intended for use against HIV-2 or other STIs. Dapivirine does not have any contraceptive properties.[4] Detailed information on dapivirine is available in the Dapivirine VR Investigator's Brochure (IB).[5]

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 vaginal gels and therefore a wealth of information was available on that dosage form. However, the dapivirine silicone elastomer VR has now been prioritized over all other dosage forms for the following reasons:

- Clinical trials have demonstrated sustained delivery of high levels of dapivirine throughout the cervicovaginal vault for up to 1 month;
- Since the ring is able to deliver drug for at least 1 month, the burden of user-dependent adherence is lower than for once daily products;

- Product acceptability studies and the experience gained from marketed VR products have established a high level of acceptance and adherence from women using VR with similar physical characteristics;
- The overall cost for the VR is relatively low;
- Minimal storage space is required for the VR when compared with once daily products.

Summaries of the safety and tolerability of dapivirine orally and vaginally as evaluated in clinical studies by IPM and Tibotec Pharmaceuticals delivered 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 matrix VR in which the drug substance is dispersed in a platinum-catalyzed cured silicone.

2.3 Nonclinical Studies of Dapivirine

2.3.1 *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.[2, 4]

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

Resistance

HIV-1 breakthrough in the presence of dapivirine was initially evaluated in studies in which cells were infected with wild-type HIV-1 laboratory strains at a high multiplicity of infection and in the presence of increasing concentrations of dapivirine. At 40 nM virus breakthrough occurred between 4 and 7 days, at 200 nM breakthrough occurred between 7 and 10 days and at 1 µM it took up to 30 days to observe virus breakthrough.

In all cases, mutations were present. Virus that selected 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.

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

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

Cross-resistance

In comparison with NVP, DLV, EFV and emivirine, dapivirine showed significantly better *in vitro* activity against laboratory and recombinant HIV strains resistant to one or more drugs of the same class. The EC_{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.

2.3.2 Condom Compatibility Studies of Dapivirine

Results from male and female condom compatibility studies, IPM 029 and IPM 033, respectively, are anticipated in 2014.

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); and
- Nitrile condoms with silicone lubricant (female condom).

The results of condom compatibility testing indicate that dapivirine-containing vaginal gel formulations (0.05%) have no deleterious effects on the integrity of male or female condoms, as indicated by tensile condom properties tested pre- and post-treatment. Two clinical condom functionality studies (one with male condoms [IPM 029] and one with female condoms [IPM 033]) were conducted with a placebo 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.

2.4 Clinical Studies

2.4.1 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-025 participants.

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

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 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
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			**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 generally safe and well-tolerated.[9] IPM has conducted a review of aggregate safety information which identifies vaginal candidiasis as a possible adverse drug reaction caused by dapivirine vaginal ring use. The 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).[6] 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).[10] Ten women underwent 7-day exposure to dapivirine Ring-002, and three women used a placebo ring for 7 days. There were no SAEs during the trial and few TEAEs. The trial results showed that the dapivirine ring was safe in healthy participants.

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

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.

2.5 Prevalence of Primary Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) Resistance Mutations

Recent data on primary NNRTI resistance from a WHO threshold surveillance study conducted between 2005-2009 categorized Kwa-Zulu Natal as having 5-15% NNRTI resistance.[13] MTN-009 found 6.5% NNRTI resistance amongst participants screening for VOICE who were already HIV positive, with 87% of those with NNRTI resistance having HIV-1 with Y181C and/or K103N.[14] In the Stanford University HIV Drug Resistance Database, which compiled data from 12,014 HIV-1 subtype C sequences, and 5831 subtype A & D sequences from treatment-naïve and NNRTI-treated persons, the following was found:[15]

Table 2: Frequency of K103N

	Treatment-Naïve	NNRTI-experienced
Subtype C	1.2%	42%
Subtypes A and D	no data	14%

Table 3: Frequency of Y181C

	Treatment-Naïve	NNRTI-experienced
Subtype C	no data	27%
Subtypes A and D	no data	18-20%

2.6 Behavioral Studies

2.6.1 Acceptability of Dapivirine VR

IPM 011 assessed the acceptability of the dapivirine VR and the placebo VR in 170 women. The trial was conducted across multiple sites in Tanzania and South Africa. The study participants found the ring to be very comfortable (95%), very easy to insert (94%) and remove (92%), and rarely were the rings felt during daily activities. All questionnaire respondents, when asked if they would be willing to use the vaginal ring if shown to be effective for HIV prevention, replied that they would use the VR.[16]

In IPM 015, at Week 12, 97% of African women reported that the dapivirine VR was comfortable and that they were willing to use the VR if it was found to be effective. Women preferred to wear the VR every day (97%) and reported that the ring did not interfere with their daily activities (89%). In terms of the male partner acceptability, 63% of women reported that their partner did not feel the ring during sex. Of those participants who reported that their partner felt the ring, only 1% reported that this might be or definitely was a problem.[11]

2.6.2 Adherence of Dapivirine VR

In IPM 011, 11% of the women experienced expulsions/removal, with the most common reason being 'menses related'. In the majority of cases (64%), the VR was washed and re-inserted.[16]

In IPM 015, perfect adherence was reported by 92% of the female participants. Perfect adherence was defined as never having the VR out for more than an entire day. Of the women who reported that the ring was out, the most common activity for expulsion was urination/defecation. The most common reason reported by participants for VR removal was cleaning. As the study progressed, more women reported removing the VR prior to sexual intercourse, 17% at week 2 and 36% by week 12.[11]

2.7 Rationale for Study Design

2.7.1 Study Design

The dapivirine VR advanced to evaluation in Phase 3 safety and effectiveness trials based on data from preclinical and early clinical safety trials. Upon demonstration of the safety and effectiveness of the dapivirine VR in the MTN-020, implementation of the follow-on trial, MTN-025, will commence.

The primary focus of MTN-025 is the collection of additional adherence and safety data further, MTN-025 will examine incidence of HIV-1 infection and explore the way in which participants adopt this biomedical prevention method and incorporate it into the context of their everyday lives.

While there are many facets to the future roll-out of ARV-based prevention that are worthy of study, including potential impacts on behavior, optimizing drug adherence, and implementation strategies for the public sector, all future approaches must be grounded in an evidence base for safe management of these drugs in healthy populations. MTN-025 will contribute to this evidence base by describing the safety outcomes with a quarterly monitoring schedule for women using an ARV-based HIV prevention intervention. Safety data will be forwarded to regulatory entities. Roll-out of ARV-based prevention in the public sector in resource-limited environments will likely require a pharmacovigilance strategy that is less costly and time-consuming than the options described here. MTN-025 will provide valuable information that will help guide the development of those strategies.

MTN-025, the HIV Open-label Prevention Extension (HOPE) trial will provide additional safety and adherence data of dapivirine (25 mg) in a silicone elastomer vaginal matrix ring (Ring-004) when inserted monthly in healthy, HIV-uninfected, not pregnant, sexually active research-experienced women should efficacy be demonstrated in MTN-020.

2.7.2 Incorporating Emergent Effective HIV-1 Prevention Strategies

As of June 2014, the United States was the only country where ARVs (the combination daily oral pill emtricitabine/tenofovir disoproxil fumarate [Truvada®]) are licensed for use as pre-exposure prophylaxis (PrEP). However, as candidate microbicides continue to demonstrate evidence of efficacy, the potential for one or more licensed HIV-1 prevention strategies in sub-Saharan Africa may soon become a reality. The HOPE Protocol Team will follow all relevant national policies regarding HIV-1 prevention and will actively consult with stakeholders in the event that an effective intervention is approved locally. Consultation with target populations, policy makers, governments and other stakeholders will be ongoing throughout the duration of study implementation and participant follow-up by study leadership, Microbicide Trial Network (MTN) Leadership and the MTN Community Working Group (CWG).

3 OBJECTIVES

3.1 Primary Objectives

1. Safety
   - To characterize the safety profile associated with the open label use of the dapivirine vaginal matrix ring (25 mg) in women

2. Study Product Adherence
   - To characterize adherence to the open label use of the dapivirine vaginal matrix ring (25 mg) in women

3.2 Secondary Objectives

1. Incidence
   - To assess incidence of HIV-1 infection

2. Drug Resistance
   - To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection

3.3 Exploratory Objectives

1. To explore participant understanding of efficacy

2. To explore ring acceptability in the context of known efficacy

3. To assess the feasibility of a quarterly follow-up visit schedule

4. To describe the genital microenvironment in women exposed to the dapivirine vaginal ring

5. To characterize the MTN-020 participants who choose not to enroll into MTN-025

4 STUDY DESIGN

4.1 Identification of Study Design

The MTN-025 trial, HOPE, is a multi-site, open-label, Phase 3B trial that will be implemented if the dapivirine VR is found to be a safe and an effective HIV prevention method in the MTN-020 trial. Eligible former MTN-020 HIV-uninfected participants will attend monthly study visits until the third month of follow-up and then quarterly visits thereafter. The study will assess the safety of and participant adherence to a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine.

4.2 Summary of Major Endpoints

Primary Endpoints:

1. Safety
   - Grade 2 AEs judged to be related to the dapivirine vaginal ring
   - Grade 3 and higher AEs
   - All serious AEs

2. Study Product Adherence
   - Residual levels of dapivirine in returned vaginal rings
   - Blood dapivirine levels

Secondary Endpoints:

1. Incidence
   - HIV-1 infection as measured by the protocol algorithm

2. Drug Resistance
   - HIV-1 drug resistance mutations among participants who acquire HIV-1, as measured by standard genotype analysis and more sensitive methods to detect low frequency drug-resistant variants

4.3 Description of Study Population

Former MTN-020 participants who are healthy, HIV-uninfected, not pregnant and meet eligibility criteria as described in Sections 5.2 and 5.3

Decliner Population: Former MTN-020 participants who decline participation in the main MTN-025 study and meet eligibility criteria as described in Sections 5.4 and 5.5

4.4 Time to Complete Accrual

The majority of former ASPIRE participants are anticipated to enroll approximately 3-6 months following site activation, see Section 10.4 for additional details.

4.5 Expected Duration of Participation

The majority of former ASPIRE participants will complete approximately 13 months of follow-up, see Section 10.4 for additional details. Follow-up may be extended beyond 13 months based on need and requirements and with the necessary approvals.

Visits may be completed within specified windows around target dates. Detailed information regarding visit windows will be described in the MTN-025 Study Specific Procedures (SSP) Manual.

4.6 Sites

Approved former MTN-020, ASPIRE, sites will participate in MTN-025, HOPE.

5 STUDY POPULATION

5.1 Selection of the Study Population

If safety and efficacy of the dapivirine vaginal ring are demonstrated in MTN-020 (ASPIRE); MTN-025 (HOPE), will be implemented as a follow-on trial. Inclusion and Exclusion Criteria, Sections 5.2 and 5.3, respectively, are used to ensure the appropriate selection of study participants for MTN-025.

Decliner Population: Former MTN-020 participants who decline participation in the main MTN-025 study, and who meet inclusion and exclusion criteria in Sections 5.4 and 5.5, will be invited to complete behavioral assessment(s).

5.1.1 Recruitment

Participants will be recruited from study site cohorts of MTN-020 participants. Efforts will be made by study sites to maintain contact with MTN-020, ASPIRE, participants

between the end of follow-up in MTN-020 and the initiation of the MTN-025 trial, HOPE, to provide MTN-020 study results and information regarding the HOPE study to participants. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use. Site community representatives should advise on these materials before they are submitted to the IRB/EC for review. Community education strategies, including group sessions, may be employed as part of participant/partner outreach.

5.1.2 Retention

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

5.2 Inclusion Criteria

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

1) Previously enrolled in MTN-020 (ASPIRE)

2) Able and willing to provide written informed consent to be screened for and to take part in the study

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

4) HIV-uninfected based on testing performed by study staff at Screening and Enrollment (per applicable algorithm in Appendix II)

5) Using an effective method of contraception at Enrollment, and intending to use an effective method for the duration of study participation; effective methods include hormonal methods (except contraceptive ring); intrauterine contraceptive device (IUCD); and sterilization (of participant, as defined in site SOPs)

6) 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

5.3 Exclusion Criteria

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

1) Study product use permanently discontinued in response to an AE or safety related concern while taking part in the MTN-020 (ASPIRE) trial

2) Per participant report at Screening:
   a) Plans to relocate away from the study site during study participation
   b) Plans to travel away from the study site for more than three consecutive months during study participation

3) Per participant report at Enrollment, currently taking Post-Exposure Prophylaxis (PEP)

   Note: PEP use at Screening is not exclusionary. Participants may be enrolled after the PEP regimen is complete and a negative HIV test is documented within 56 days of providing informed consent for Screening.

4) With the exception of MTN-020 (ASPIRE), participation in any other research study involving drugs, medical devices, vaginal products, or vaccines, within 60 days of enrollment

   Note: Participation in the 'Decliner Population' does not preclude MTN-025 full study participation in the future.

5) Is pregnant at Screening/Enrollment or planning to become pregnant in the participant's anticipated study participation period
   Note: A documented negative pregnancy test performed by study staff is required for inclusion; however a self-reported pregnancy is adequate for exclusion from screening/enrollment into the study.

6) Currently breastfeeding

7) Diagnosed with urinary tract infection (UTI), pelvic inflammatory disease (PID), STI or reproductive tract infection (RTI) requiring treatment per WHO guidelines

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

8) At Screening, has a clinically apparent Grade 3 pelvic exam finding (observed by study staff) as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009), Addendum 1-Female Genital Grading Table for Use in Microbicide Studies

   Note: Otherwise eligible participants with exclusionary pelvic exam findings may be enrolled after the findings have improved to a non-exclusionary severity grading or

resolved. If improvement to a non-exclusionary grade or resolution is documented within 56 days of providing informed consent for screening, the participant may be enrolled.

9) Has any of the following laboratory abnormalities at Screening Visit:
   a) Aspartate aminotransferase (AST) or alanine transaminase (ALT) ≥ Grade 3*
   b) Creatinine ≥ Grade 3*
   c) Hemoglobin ≥ Grade 3*
   d) Platelet count ≥ Grade 3*
   e) Pap result ≥ Grade 3 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009)

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

   Note: Women with a documented normal result within the 12 months prior to enrollment need not have Pap smear during the screening period. Need for a repeat Pap within 6 months does not preclude enrollment prior to that result becoming available.

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

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

5.4 Inclusion Criteria- MTN-025 Decliner Population Only

MTN-025 Decliner Population participants must meet all of the following criteria to be eligible for inclusion in the study:

1) Able and willing to provide informed consent
2) Participated in MTN-020 (ASPIRE)
3) Declines MTN-025 (main) study trial participation
4) Able and willing to perform the Decliner Population study procedures

5.5 Exclusion Criteria- MTN-025 Decliner Population Only

MTN-025 Decliner Population participants who meet the following criteria will be excluded from the study:

1) Has any condition that, in the opinion of the Investigator of Record (IoR)/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

5.6 Co-enrollment Guidelines

As indicated in Section 5.2 and 5.3, participants should not take part in other research studies involving drugs, medical devices, vaginal products or vaccines after the Screening Visit and while taking part in this study. Each site will be responsible for defining procedures for management and prevention of co-enrollment prior to initiation.

Exceptions to this guideline may be made for participants to co-enroll in the following types of studies at the discretion of the IoR/designee:

- Participants may take part in ancillary studies approved by the MTN-025 Protocol Chair
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-positive persons
- Participants who become pregnant may take part in observational studies, including pregnancy registries approved by the MTN-025 Protocol Chair

Should any participant report or should study staff discover concurrent participation in any other study after enrolling in MTN-025, the IoR/designee will consult the Protocol Safety Review Team (PSRT) regarding ongoing product use and other potential safety considerations associated with co-enrollment.

6 STUDY PRODUCT

6.1 Regimen

All participants will receive a vaginal ring containing 25 mg of dapivirine to be worn monthly. One new ring will be inserted each month. Participants will attend monthly clinic visits until month three and then will present to the clinic at quarterly visits thereafter. Participants are able to visit the clinic for any reason in between the scheduled visits.

6.2 Administration

The participant will self-insert the study VR monthly. Study participants will be reminded of proper VR insertion and removal procedures at the Enrollment Visit and as needed at subsequent visits. Details on administration (ring insertion, removal, procedures in the event of expulsion or loss) will be provided in the MTN-025 SSP Manual.

6.3 Study Product Formulation

The study VR is an off-white, flexible ring containing 25 mg of dapivirine dispersed in a platinum-catalyzed-cured silicone matrix. The ring dimensions are as follows: 56 mm and 7.7 mm, outer diameter and cross-sectional diameter, respectively.

The ring is designed to provide sustained release of drug over a minimum period of one month.

6.3.1 Dapivirine VR

Dapivirine 0.3125% (w/w) is dispersed in a flexible, opaque, cured silicone VR delivery device. The VR will contain 25 mg of dapivirine. The dapivirine VR optimally should be stored in the site pharmacy at 20°C to 25°C, with allowable excursions between 15°C to 30°C.

6.4 Supply and Accountability

6.4.1 Supply

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

6.4.2 Study Product Dispensing

Study VRs are dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. Dispensing takes place on the day of enrollment and at each scheduled follow-up visit, except at the Product Use End Visit and Study Exit/Termination Visit.

During each of the monthly clinic visits participants will receive a new ring. If the participant is unable to attend her next scheduled visit it is up to the discretion of the IoR to provide an additional ring(s). All such circumstances must be documented fully by the IoR/designee as described in the MTN-025 SSP Manual.

When participants enter the quarterly follow-up phase, they will be dispensed three rings at each study visit or be given the option of returning to the site pharmacy or the clinic (based on site dispensing capacity) each month to obtain a new vaginal ring each month (e.g., if they do not feel comfortable having a supply of two additional unused rings at home). Participant's preference regarding product dispensation and their choice will be documented.

The pharmacist will only dispense one ring per month or up to three rings per quarter depending on the participant's regimen. If a participant requires an additional ring for any reason, at a time other than when she is scheduled to receive one, additional product may be dispensed at the discretion of the IoR.

6.4.3 Accountability

Each CRS Pharmacist of Record (PoR) is required to maintain a complete record of all study product received and subsequently dispensed. All unused study products must be returned to the MTN Pharmacist after the study is completed or terminated unless otherwise instructed by the MTN Pharmacist. The procedures to be followed are provided in the MTN-025 Pharmacist Study Product Management Procedures Manual.

All study product dispensed to a participant must be documented by the clinic staff when it is returned. This includes ring(s) 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

As per Section 9, study product use for a participant may be temporarily held or permanently discontinued. Study product must be retrieved within 24 hours and returned to the clinic when product use is permanently discontinued for HIV seroconversion or held temporarily due to potential HIV seroconversion (see Table 5 below). Additional study product retrieval specifications in response to product holds, discontinuations for other reasons, or IoR discretion, can be found in the table below. Study product retrieval may occur either by the participant returning the VR (used and unused) to study staff within the specified timeframe or by study staff conducting outreach to retrieve the product from the participant (e.g., at her home).

Table 4: Retrieval of Study Product

Condition	Timeframe for Retrieval
• Permanent discontinuation due to HIV seroconversion • Temporary hold due to potential HIV seroconversion	Within 24 hours
• Permanent discontinuation for any other reason or IoR discretion • Temporary hold due to pregnancy	Within 5 working days
• Temporary hold for reasons other than pregnancy with expected duration of more than 7 days	Within 7 working days

If product has not been retrieved within the timeframe specified in the table above, 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, to protect participant safety, study product(s) may be retrieved from participants 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 due to seroconversion, pregnancy or other safety related concerns, if the study product(s) are not retrieved within timeframe noted, the MTN-025 PSRT must be informed.

For each participant, all VRs remaining in the participant's possession should be retrieved at the Study Exit/Termination Visit. If the participant does not bring her remaining VR(s) to this visit, study staff must arrange to retrieve the ring(s) within 5 business days.

The PoR will document all unused product returns and store returned unused study products in designated areas within the study pharmacy.

6.5 Concomitant Medications

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

6.6 Use of Intravaginal Medications and Practices

Concomitant use of devices such as diaphragms, menstrual cups, and cervical caps, will be discouraged. Use of contraceptive VRs is prohibited. Products and practices including the use of spermicides, vaginally applied medication, douches, lubricants,

tampons, etc., are permitted. Use of intravaginal medications and practices will be captured.

6.7 Condoms

All participants will be offered condoms. Condoms are highly effective in preventing the sexual transmission of HIV and reducing the risk other STIs, including infections transmitted by genital secretions, and to a lesser degree, genital ulcer diseases.[17-19] Study staff may also offer guidance on the use of the female condoms upon participant request, see MTN-025 SSP for additional details.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is provided in Appendix I. Follow-up study visits may take place on-site, in a participant's home, or at other community-based locations, depending on site capacity and site/participant preference. If genital symptoms are reported during an off-site visit, the participant is instructed to report to the on-site clinic for a clinical evaluation. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites, including the conduct of off-site study visits and the follow-up schedule for participants who enroll after the prime accrual period are provided in the MTN-025 SSP Manual available at http://www.mtnstopshiv.org/studies.

7.1 Pre-Screening

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

7.2 Screening Visit

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

Table 5: Screening Visit

Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent for screening • Assign a Participant Identification (PTID) Number • Assess eligibility • Collect locator information • Provide reimbursement for study visit • Schedule next visit*
Behavioral		• Provide counseling – Contraceptive – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Obtain medical and menstrual history • Obtain concomitant medications • Conduct a physical examination • Perform a pelvic exam • Offer contraceptives* • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – human chorionic gonadotropin (hCG) – Nucleic Acid Amplification Test (NAAT) for GC/CT – Urine culture*Ŧ
	Blood	• Collect blood – HIV-1 serology – Complete blood count (CBC) with platelets – Chemistries – Syphilis serology
	Pelvic	• Collect pelvic specimens – Rapid test for Trichomonas – Pap smear interpretation*
Study Product/ Supplies		• Offer condoms

* if indicated; Ŧ per local standard of care

7.3 Enrollment Visit (Day 0)

The Enrollment Visit must be completed within 56 days of the Screening Visit.

Note: All enrolled participants will receive regular individual HIV counseling, condoms (if participant is willing to accept them), risk reduction counseling, and treatment for STIs as part of their clinic visits. If other new prevention strategies are found to be efficacious and are incorporated into the national HIV prevention policies, study participants will be counseled about these interventions, and either be offered these interventions by the site or referred to local centers with appropriate expertise, in accordance with WHO/UNAIDS guidelines and local practice and stakeholder consultation.

Table 6: Enrollment Visit

Enrollment Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent for enrollment • Reassess and confirm eligibility • Review/update locator information • Provide reimbursement for study visit • Schedule next study visit*
Behavioral		• Conduct behavioral assessment • Provide counseling – Contraceptive – HIV/STI risk reduction – HIV pre- and post-test – Protocol adherence
Clinical		• Update medical and menstrual history • Update concomitant medications • Disclose available test results • Perform a physical examination* • Perform a pelvic exam* • Offer contraceptives* • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – Urine culture*Ŧ – NAAT for GC/CT*
	Blood	• Collect blood – Plasma archive – HIV-1 serology
	Pelvic	• Collect pelvic specimens – Vaginal fluid (self-collected) – Rapid test for Trichomonas*
Study Product/Supplies		• Offer condoms • Provision of study VR use instructions • Provision of study VR(s) • Insertion of one study VR • Digital exam by clinician to check VR placement*

* if indicated; Ŧ per local standard of care

7.4 Follow-up Visits

7.4.1 Months 1 and 2

Procedures listed below will occur at study months 1 and 2.

Table 7: Follow-up Visits: Months 1 and 2

Follow-up Visits: Months 1 and 2		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit
Behavioral		• Provide counseling (modified, if necessary) – Contraceptive – Protocol adherence – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Review/update medical and menstrual history • Disclosure of available test results • Record/update AEs • Review/update concomitant medications* • Offer contraceptives* • Perform a physical examination* • Perform a pelvic examination* • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – NAAT for GC/CT* – Urine culture*Ŧ
	Blood	• Collect blood – HIV-1 serology – Chemistries* – Syphilis serology*
	Pelvic	• Collect pelvic specimens – Vaginal fluid (self-collected) – Rapid test for Trichomonas*
	Study Product	• Adherence assessment(s): Returned study VR
Study Product/Supplies		• Offer condoms • Removal and collection of used/unused study VR • Provision of VR use instructions* • Provision of study VR • Digital exam by clinician to check VR placement*

* if indicated; Ŧ per local standard of care

7.4.2 Quarterly Visits

Procedures listed below will occur at quarterly visits (i.e., Months 3, 6, 9),until the Product Use End Visit (PUEV).

Table 8: Quarterly Visits

Follow-up Quarterly Visits		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit
Behavioral		• Conduct behavioral assessment • Conduct social harms assessment • Provide counseling (modified, if necessary) – Contraceptive – Protocol adherence – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Perform physical examination* • Disclosure of available test results • Record/update AEs • Perform a pelvic examination* • Offer contraceptives* • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – NAAT for GC/CT* – Urine culture*Ŧ
	Blood	• Collect blood – HIV-1 serology – Plasma sample for DPV testing and archive – Chemistries* – Syphilis serology*
	Pelvic	• Collect pelvic specimens – Vaginal fluid (self-collected) – Rapid test for Trichomonas*
	Study Product	• Adherence assessment(s): Returned study VR
Study Product/Supplies		• Offer condoms • Removal and collection of used/unused study VR(s) • Provision of VR use instructions* • Provision of study VR(s) • Digital exam by clinician to check VR placement*

* if indicated; Ŧ per local standard of care

7.4.3 Product Use End Visit (PUEV)

Participants will undergo the following procedures at the PUEV.

Table 9: PUEV

PUEV		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit
Behavioral		• Conduct behavioral assessment • Conduct social harms assessment • Provide counseling (modify, if necessary) – Contraceptive – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Perform a physical examination • Perform a pelvic examination • Disclosure of available test results • Record update AEs • Offer contraceptives* • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – NAAT for GC/CT – Urine culture*Ŧ
	Blood	• Collect blood – HIV-1 serology – Syphilis serology – Chemistries – CBC with platelets – Plasma sample for DPV testing and archive
	Pelvic	• Collect pelvic specimens – Vaginal fluid (self-collected) – Rapid test for Trichomonas
	Study Product	• Adherence assessment(s): Returned study VR
Study Product		• Offer condoms • Removal and collection of used/unused study VR

* if indicated; Ŧ per local standard of care

7.4.4 Study Exit/Termination Visit

The Study Exit/Termination Visit is to be scheduled approximately 4 weeks after the PUEV.

Table 10: Study Exit/Termination Visit

Study Exit/ Termination Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit*
Behavioral		• Conduct behavioral assessment • Provide counseling – Contraceptive* – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Disclosure of available test results • Record/update AEs • Offer contraceptives* • Perform a physical examination* • Perform pelvic examination* • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – NAAT for GC/CT* – Urine culture*Ŧ
	Blood	• Collect blood – HIV-1 serology – Plasma sample for DPV testing and archive
	Pelvic	• Collect pelvic specimens – Vaginal fluid (self-collected) – Rapid test for Trichomonas*
Study Product		• Offer condoms

* if indicated; Ŧ per local standard of care

7.5 MTN-025 Decliner Population

7.5.1 MTN-025 Decliner Population: Screening and Enrollment Procedures

Former ASPIRE participants who decline or express no interest in joining the main MTN-025 trial, may opt to take part in the MTN-025 Decliner Subset. Multiple visits may be conducted to complete all required procedures, as necessary. See Section 7.8, *Behavioral Evaluations* for additional details.

Table 11: Screening and Enrollment Procedures

Screening and Enrollment	
Component	**Procedures**
Administrative and Regulatory	• Confirm eligibility • Obtain written informed consent • Collect demographic data • Provide reimbursement for study visit
Behavioral	• Administer behavioral assessment • Conduct in-depth interview (IDI)*

*=if indicated

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

7.6.1 Participants Who Become Infected with HIV

Participants who become infected with HIV are offered the option to continue follow-up visits per their original study schedule until their originally scheduled study exit date. All participants who become infected with HIV while on study product will be offered enrollment in MTN-015, the MTN Seroconverter Study. Participants are offered enrollment in MTN-015 (http://www.mtnstopshiv.org/studies) at the visit when seroconversion confirmation test results are discussed with the participant.

For those participants who choose to be maintained in MTN-025 follow-up, regardless of co-enrollment in MTN-015, protocol-specified procedures for MTN-025 will continue, except the following:

- HIV serology, HIV pre- and post-test counseling
- Provision of VR, instructions, product adherence counseling
- Complete blood count
- Chemistries
- Scheduled HOPE Study Exit/Termination Visit

For participants who delay or decline enrollment in MTN-015, the following procedures are being completed as part of the MTN-025 study; these procedures are discontinued immediately if the participant enrolls in MTN-015:

- Plasma collection
- CD4+ T cell count
- HIV-1 RNA PCR
- HIV-1 Genotyping (standard resistance testing)

The aforementioned procedures are performed at the following time points:

- Plasma collection, CD4+ T cell count and HIV-1 RNA PCR will be performed upon each instance of a positive HIV rapid test(s) during follow-up
- Plasma collection, CD4+ T cell count and HIV-1 RNA PCR will be performed at the clinic visit immediately following confirmation of an HIV-infection and every three months thereafter for the remaining follow-up period, or as indicated
- HIV-1 Genotyping (standard resistance testing) will be performed on the stored plasma closest to the time of confirmed HIV-1 infection. It may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center.

Please reference the MTN-025 SSP for additional details.

7.6.2 Participants Who Become Pregnant

All protocol-specified study procedures will continue except the following:

- Provision of VR, product use instructions, and adherence counseling. Product use may be resumed after birth or other termination of the pregnancy, as evidenced by a negative pregnancy test performed by study staff, provided the participant is not breastfeeding. VR use should not be resumed earlier than 2 weeks after a 1st trimester loss, or earlier than 4 weeks after 2nd trimester (or later) pregnancy loss or delivery. A pelvic exam must be performed prior to resumption to confirm the absence of any findings that would contraindicate resumption, in the opinion of the IoR/designee.
- Pelvic examination as well as associated procedures, and vaginal fluid collection, after 24 weeks of pregnancy, unless the participant indicates comfort with continuing vaginal procedures post 24 weeks. See MTN-025 SSP Manual for additional guidance.

A participant who becomes pregnant during the course of study participation may be offered participation in MTN-016, the Prevention Agent Pregnancy Exposure Registry.

7.6.3 Participants Who Temporarily Hold or Permanently Discontinue Study Product Use

All protocol-specified study procedures will continue except the following:

- Provision of VR, product use instructions, and adherence counseling

In the event that a participant permanently discontinues study product early, the Adherence and Acceptability Assessments will be administered according to guidance provided from the protocol team. See the MTN-025 SSP Manual for additional guidance.

Guidance related to permanent discontinuation of study product, including consultation with the PSRT, is included in Section 9.

7.6.4 Interim Visits

Interim visits may be performed at any time during the study, for the following or other reasons:

- For administrative reasons, e.g., a participant may have questions for study staff, or may need to re-schedule a follow-up visit.
- For product-related reasons, including to provide participants with a replacement or additional vaginal ring.
- In response to AEs and/or SAEs. When interim contacts or visits are completed in response to participant reports of AEs and/or SAEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care (see also Section 9).
- For interim STI counseling and testing in response to STI symptoms.
- For interim HIV counseling and testing in response to participant report of symptoms consistent with acute seroconversion or presumed exposure to HIV
- To provide participants with the results of confirmatory HIV test results, per the algorithm in Appendix III.
- For other reasons at participant request, e.g., social harm.

All interim contacts and visits will be documented in participants' study records and on CRFs, if applicable.

7.7 Final Contact

Since participants' Study Exit/Termination Visit include laboratory testing for HIV, a final contact may be required to provide her additional study test results, and post-test counseling, if needed. In addition, for participants who become pregnant during study participation, an additional contact may be required to ascertain the participant's pregnancy outcome. Study sites may complete these contacts at the study site or at

community-based locations, depending on site capacities and site and participant preferences. All final contacts will be documented in participant study records.

7.8 Behavioral Evaluations

The following attitudes and behaviors, including the endpoints to assess exploratory objectives, will be assessed either via Audio Computer-Assisted Self Interviewing or CRFs. Additionally, a subset of eligible participants at selected sites will be asked to participate in in-depth interviews and/or focus group discussions (IDI and/or FGDs) at a predetermined time point. These will be conducted by trained interviewers/facilitators to gain further insight on the following behavioral and attitudinal issues:

- Attitudes and understanding of VR efficacy
- VR acceptability and attitudes towards combination prevention (i.e., use-related attributes and preferences, access, cost, health system delivery)
- Motivations for joining or declining participation in research study
- Reports of products storage and use
- Perceived feasibility of study visit regimen
- Sexual activity, including condom use
- Vaginal practices

MTN-025 Decliner Population

Former ASPIRE participants who decline or express no interest in joining the MTN-025 trial either prior to screening or prior to enrollment, will be invited to complete behavioral assessment(s), which may include IDI(s) to explore reasons for disinterest, indviduals who are found eligible and who take part are referred to as the MTN-025 Decliner Population.

7.9 Adherence Counseling

Study product adherence counseling will be provided as a component of the Protocol Adherence Counseling 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.

7.10 Clinical Evaluations and Procedures

Physical exams will include the following assessments:

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

**may be omitted after the Screening Visit*

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

The required sequence of procedures and specimen collection performed during pelvic exams will be specified in the MTN-025 SSP Manual.

Participants for whom there is documentation of surgical sterilization may have contraceptive counseling omitted, in accordance with any relevant site SOPs.

7.11 Laboratory Evaluations

Local Laboratory

- Urine
  - hCG
  - NAAT for GC/CT
  - Culture (per local standard of care)

- Blood
  - Plasma archive (stored at site until notified by MTN Laboratory Center (LC)
  - Plasma (stored at site until notified by MTN LC)
  - Syphilis serology
  - HIV serology
  - CBC with platelets
  - Chemistries
    - Creatinine, AST, ALT
- Pelvic
  - Rapid test for Trichomonas
  - Vaginal fluid

Laboratory Center

- Blood
  - HIV-1 confirmatory testing as needed (see Appendix III)
  - Drug concentration in blood
  - HIV drug resistance

- Pelvic
  - Vaginal fluid for candidate biomarkers of safety, adherence and efficacy, HIV exposure and antiretroviral resistance, and/or genital microflora, as needed

IPM or MTN Designated Laboratory:

- Study Product- Vaginal Ring
  - Adherence assessment(s)

7.12 HIV Infection (Secondary Endpoint) Determination

All study sites will perform HIV testing per the algorithm in Appendix III for purposes of secondary endpoint determination. Prior to study initiation, all sites will have validated this algorithm in accordance with the policies described in the MTN Manual of Operational Procedures (MOP) (http://www.mtnstopshiv.org/node/187). All sites will participate in ongoing proficiency testing of their HIV testing procedures throughout the course of the study. The HIV test kits used at each site are pre-approved by the MTN LC; at each testing time point when rapid tests are used at least one FDA-approved rapid test kit is used. All confirmatory testing is performed using FDA-approved test kits.

HIV DNA is not routinely used in MTN-025 for HIV diagnosis but may be used when requested by the MTN LC.

The MTN LC will verify HIV testing performed at the study site laboratories for purposes of eligibility determination and secondary endpoint ascertainment as follows:

- The MTN LC will test Study Entry, PUEV, and scheduled Termination Visit specimens from a 10% random sample of participants enrolled at each site for evidence of HIV infection using FDA-licensed tests. Study Entry specimens are collected at participants' Enrollment Visits. If any false-negative local laboratory results are identified, the LC will test the respective Study Entry, PUEV and scheduled Termination Visit specimens from all enrolled participants from that Clinical Research Site.

- The MTN LC will test the Study Entry and Seroconversion specimens from all study participants identified by the local laboratories as having become infected with HIV during the study follow-up period. The LC will also test matched Study Entry and Follow-Up specimens from a random sample of uninfected participants (equal to the number of seroconversions). Study Entry specimens are collected at participants' Enrollment Visit. Seroconversion specimens are collected at the schedule specified in Section 7.6.1. All specimens will be tested for evidence of HIV infection using FDA-licensed tests. For all seroconverters, Study Entry specimens also will be confirmed.

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

In addition to all of the above, an endpoint adjudication committee will provide guidance on endpoint determination to the Protocol Team on an as needed basis. See the MTN MOP (http://www.mtnstopshiv.org/node/187) for detailed information on the composition, roles, and responsibilities of the endpoint adjudication committee.

7.13 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical laboratory practice (http://apps.who.int/tdr/publications/tdr-research-publications/gclp-web/pdf/gclp-web.pdf), in accordance with current US Division of AIDS (DAIDS) Laboratory Requirements, MTN-025 Study Specific Procedures Manual

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

7.14 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)

7.15 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 U.S. Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH). All biological specimens will be transported using packaging mandated by US Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazard waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

Site IoRs/designees are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Co-Chairs, DAIDS Medical Officer, Protocol Safety Physician(s), IPM Representative, and SDMC Clinical Affairs Safety Associate will serve as the Protocol Safety Review Team (PSRT). The MTN SDMC prepares routine AE and clinical data reports for review by the PSRT, which meets via conference call approximately once per month or as needed throughout the period of study implementation to review safety data, discuss product use management, and address any potential safety concerns.

8.2 Clinical Data Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are the first layer of this tiered system and 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.

During the trial, the PSRT will review safety reports and conduct calls to review the data as appropriate. The content, format and frequency of the safety reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to these routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to the MTN with expertise in the fields of microbicides, biostatistics, or medical ethics may be invited to join the PSRT safety review.

After the product use and the final safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the MTN-025 PSRT.

A Study Monitoring Committee (SMC) has study oversight and is charged with reviewing participant safety data as no Data Safety Monitoring Board (DSMB) is planned for this study, see Section 10.7.1 for additional details.

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 participants at the time of enrollment. Enrollment is defined as once a participant has provided written informed consent for enrollment and it has been determined she is eligible for the study (based on IoR or designee sign-off after all protocol-specified inclusion/exclusion criteria have been assessed). The term “investigational product” for this study refers to the vaginal ring.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience. In cases of potentially life-threatening events, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where a study clinician is based, and to request that the clinician be

contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be recorded on study CRFs. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes.

Study site staff will document in source documents all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product.

Study staff will also report on CRFs the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs, including STIs
  - Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs
  - Genital bleeding clinically assessed to be expected is not an AE
- All AEs of severity Grade 2 or higher
- All serious AEs
- All AEs that result in permanent discontinuation of study product use
- All lab test abnormalities specified in the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), that are not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements per Section 8.3 below; this includes all congenital anomalies identified in the fetuses and/or infants of study participants

AE severity and laboratory tests will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), except that asymptomatic BV and asymptomatic candidiasis will not be reportable AEs. In addition, changes in genital bleeding judged to be related to a woman's contraceptive use will not be considered an AE, nor will a pelvic exam be required for follow-up. 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.

All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the exit visit, the status/outcome of the AE should be updated to “continuing at end of study participation” and the AE Log form should be re-faxed to SCHARP DataFax. For any serious or expedited AEs (SAEs/EAEs) that are continuing at a participant’s study exit visit, the IoR/designee must establish a clinically appropriate follow-up plan for the AE. At a

minimum, the SAE/EAE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the study exit visit. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The PSRT may advise study staff as to whether any additional follow-up may be indicated on a case by case basis. For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE Log CRFs based on the re-assessments.

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
- *Not Related:* There is not a reasonable possibility that the AE is related to the study agent

8.4 Expedited Adverse Event Reporting Requirements

8.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at

http://rsc.tech-res.com/safetyandpharmacovigilance/. For each study participant, expedited AE reporting will be undertaken throughout the scheduled duration of follow-up, i.e., from the time of Enrollment through study termination.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov 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 agent for which expedited reporting is required is the dapivirine VR
- For all SAEs submitted, sites must file an initial report and an update to IPM and the DAIDS Medical Officer with the final or stable outcome unless the initial SAE submitted had a final or stable outcome noted already

8.4.3 Grading Severity of Events

The grading of severity of events and the reporting period will be the same as for all AEs, as described in Section 8.3.1. The most current Division of AIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification, August 2009) and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification, 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 enrolled and continues up through the participant's final study visit (Study Exit/Termination Visit).
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.5 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the PSRT and responsible site ECs/IRBs according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Each site will provide such care and counseling in accordance with standardized guidance provided in the MTN-025 SSP Manual. While maintaining participant confidentiality, study sites may engage their community advisory boards (CABs) in exploring the social context surrounding instances of social harm.

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 ECs/IRBs in accordance with ECs/IRB requirements.

9 CLINICAL MANAGEMENT

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

9.1 Grading System

AE severity grading is described in Section 8.3.3.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

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

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

- Acquisition of HIV infection; such participants will not resume product use at any time. The study VR should be held beginning immediately upon recognition of the first reactive rapid HIV test. If via the algorithm in Appendix III the participant is determined to be HIV-uninfected, she may resume product use. The IoR/designee must permanently discontinue the study VR if HIV infection is confirmed.
- Allergic reaction to the study VR.

A participant will be temporarily held from study VR for any of the following reasons:

- A reactive rapid HIV test.
- Pregnancy. A participant who becomes pregnant may resume product use after giving birth or other pregnancy outcome, as evidenced by a negative pregnancy test performed by study staff, provided the participant is not breastfeeding. A pelvic exam must be performed prior to resumption to confirm the absence of any findings that would contraindicate resumption, in the opinion of the IoR/designee.
- Breastfeeding. Product use may resume when the participant reports complete cessation of breastfeeding.
- Report of use of PEP for HIV exposure. The participant may resume product use when she reports completion of PEP and is confirmed HIV-uninfected based on testing performed at the study site per the algorithm in Appendix III.
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee. The IoR/designee must consult the PSRT on all temporary product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation. If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time.

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

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

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

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

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

9.5 Other Clinical Findings

The IoR/designee should manage STI/RTI per local guidelines or current WHO guidelines, available at http://www.who.int/en/.

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. Observed single dose treatment should be provided whenever possible, per clinician discretion. When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible.

- Study VR need not be 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 hold is warranted, consultation with the PSRT is required.

If a suspected finding is reported by a participant between scheduled visits, an interim visits may be scheduled at the discretion of the site investigator. Note: C**hanges in genital bleeding does not necessitate a pelvic exam for follow-up.**

Management of genital events observed at scheduled or interim visits will be in accordance with the following:

Superficial epithelial disruption (abrasion/peeling)

- Continue study VR use
- Perform naked eye evaluation
- Re-evaluate by speculum examination in 3-5 days
- If condition worsens, temporarily hold study VR use and consult the PSRT; otherwise continue study VR use

Deep epithelial disruption (ulceration)

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

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

- Continue study VR use
- Perform naked eye evaluation
- If asymptomatic, re-evaluate at next regularly scheduled visit
- If symptomatic, re-evaluate by speculum examination in 3-5 days
- If worsened significantly, temporarily hold study VR use and consult the PSRT; otherwise continue study VR use

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

- Temporarily hold study VR
- Perform naked eye evaluation
- Re-evaluate in 3-5 days and resume study VR use if resolved
- If unresolved at 3-5 days, re-evaluate within 2-3 days. If resolved at that time may resume use. If unresolved at this second reevaluation, continue temporary

product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard

Unexpected genital bleeding

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

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

- Temporarily hold study VR
- Evaluate for GC/CT; consider syndromic management, pending results of testing and per clinician discretion
- If GC/CT detected, provide or prescribe treatment
- Reevaluate in 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
- Further evaluation or treatment per clinician discretion

Genital ecchymosis

- Continue study VR use
- Perform naked eye evaluation
- Further evaluation or treatment per clinician discretion

The study product 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, notification of the PSRT is required.

9.6 HIV Infection

A participant who has a positive test for HIV must have study product held, but will not be withdrawn from the study. If the participant is subsequently determined to be HIV-uninfected according to the algorithm in Appendix III, study product may be resumed. If HIV infection is confirmed, study product will be permanently discontinued by the IoR/designee. Participants identified as infected with HIV are managed or referred for management according to the local standard of care. These participants are also offered participation in MTN-015, the MTN Seroconverter Study, which also includes provisions for the clinical management and/or referral of participants infected with HIV.

The care provided at the referral sites is at a level that meets or exceeds the community standard for HIV care. Written SOPs for referral for HIV care and treatment are in place

at each study sites. All study site investigators have identified facilities offering psychological and social services and medical care, including antiretroviral therapy (ART), to people infected with HIV-1 in the study countries. Some of the research sites are part of health care institutions that provide HIV care and support, and can refer women to those services. Other sites have established referral agreements with programs to expand access to ART.

At every study visit, study staff will actively follow-up on prior referrals to HIV care and support services, to determine whether the participant sought the care to which she was referred, the outcome of the referral, and whether additional referrals are needed. All follow-up actions, outcomes, counseling, and plans for next steps are documented in participant study records. Results of study laboratory testing may be helpful in clinical management; these results are provided to the participant and her medical provider as soon as they are available.

9.7 Pregnancy

A participant who becomes pregnant at any time during the study must have study product temporarily held, but will not be withdrawn from the study. Every effort will be made to have the study participant continue in modified follow-up until her study termination visit or pregnancy outcome is ascertained. 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.

Participants who become both pregnant and HIV-infected will have expedited HIV-1 resistance testing performed at the MTN LC to provide information about possible resistance that might impact the efficacy of ART regimens to reduce mother-to-child HIV-1 transmission. The participant will be referred to local providers for antenatal care, and prevention of mother-to-child transmission services. HIV testing for infants is provided by the study if not otherwise accessible by the participant.

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

All pregnancies will be followed until a pregnancy outcome can be ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). This includes participants who are pregnant at the Study Exit/Termination Visit. Pregnancy outcomes are reported on relevant CRFs.

9.8 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. The PSRT must be notified of all terminations conducted per IoR discretion. Participants also may be withdrawn if the study sponsors, 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 will be 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 Phase 3B, open-label, multi-site trial. A sample size of approximately 1000-2500 participants will be followed for approximately 13 months, with approximately 12 months of study product use. The two main goals of the trial are:

1. To characterize the safety profile associated with the open label use of the dapivirine vaginal matrix ring (25 mg) in women

2. To characterize adherence to the open label use of the dapivirine vaginal matrix ring (25 mg) in women

Secondary objectives of the study include assessing the incidence of HIV-1 infection and frequency of HIV-1 drug resistance in women who acquire HIV-1 infection.

10.2 Study Endpoints

10.2.1 Primary Endpoints

1. Safety
   - Grade 2 AEs judged to be related to the dapivirine vaginal ring
   - Grade 3 and higher AEs
   - All serious AEs

2. Study Product Adherence
   - Residual levels of dapivirine in returned vaginal rings

- Blood dapivirine levels

10.2.2 Secondary Endpoints

1. Incidence
   - HIV-1 infection as measured by the protocol algorithm

2. Drug Resistance
   - HIV-1 drug resistance mutations among participants who acquire HIV-1, as measured by standard genotype analysis and more sensitive methods to detect low frequency drug-resistant variants

10.3 Sample Size

We expect between 1000 and 2500 participants to enroll in this study. The final number is dependent upon the proportion of ASPIRE participants who are eligible and choose to enroll into MTN-025, HOPE. Power is discussed with the primary analyses as appropriate.

10.4 Participant Accrual, Follow-up and Retention

The majority of former ASPIRE participants are anticipated to enroll within the first 3-6 months after site activation, however this period could be shorter or longer depending upon accrual rates. It is anticipated that the study will close to accrual 4 months ahead of the anticipated closure of the study. Based upon the timing of participant enrollment, follow-up may last approximately 4-13 months. Follow-up may be extended beyond 13 months based on need and requirements and with the necessary approvals.

10.5 Blinding

This is an open-label and unblinded trial.

10.6 Data and Safety Monitoring Procedures

10.6.1 Study Monitoring Committee

In addition to the safety monitoring done by the PSRT (described in Section 8), the MTN SMC will be responsible for study oversight by conducting interim reviews of study progress, including rates of participant accrual, participant retention, protocol and intervention adherence, data quality, laboratory quality and completion of primary and secondary endpoint assessments. Since MTN-025 is not subject to DSMB review, the SMC also will review participant safety data, as specified in the MTN Manual of Procedures. These reviews will take place approximately every 6 months and as needed.

At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The SMC may consider recommending termination of this study if recruitment is lower than targeted, or if study data quality is poor. If at any time, a decision is made to discontinue participants, IPM, after consultation with the protocol team, will inform the US Food and Drug Administration (FDA). The Site PIs will notify the responsible ECs expeditiously.

10.6.2 Monitoring Quality of Study Conduct Operational Characteristics and Implementation

The study may be terminated or modified for poor accrual/recruitment, adherence/product use, and/or retention. Regular reports will be provided to the SMC that outline the potential impact on the study's ability to meet its objectives if there are deviations from the statistical design in terms of accrual/recruitment, adherence/product use, retention, and/or low HIV acquisition rate.

10.7 Primary Analyses

10.7.1 Primary Safety Analysis

Consistent with the primary safety objective, this analysis will characterize the safety profile for the overall population.

Adverse events will be analyzed using MedDRA preferred terms. The number and percentage of participants experiencing each specific AE will be tabulated by severity and by relationship to treatment regimen. For the calculations in these tables, each participant's AE will be counted once under the maximum severity or the strongest recorded causal relationship to study product.

All AEs will be grouped by body system and a confidence interval for the incidence of each AE will be calculated overall and by arm. Finally, a listing of EAEs reported to the DAIDS Safety Office will provide details of the event including severity, relationship to study product, onset, duration and outcome.

Note that all of the above summaries will be calculated under the intention-to-treat (ITT) principle. However, participants off study product and/or those who are non-adherent that are included in these analyses could potentially lower the rate of safety and toxicity endpoints. Therefore, a 'per-protocol' analysis, where time off product is excluded from the analysis, will be used to explore the sensitivity of the conclusions obtained with the safety analysis under the ITT principle.

Assuming between 1000 and 2500 participants are enrolled with an average of 11 months of follow-up per participant, we expect between 917 and 2300 person-years of follow-up during this study. The assumed 11-month average follow-up reflects both loss to follow-up and staggered entry.

10.7.2 Primary Adherence Analysis

For the primary study aim related to adherence, participants will be categorized as adherent if drug is detected in all quarterly plasma samples when participants are not on a product hold and the proportion of adherent participants with a 95% confidence interval will be reported.

In an effort to understand more complicated adherence patterns, secondary analyses for adherence will be performed. Similar analysis of residual drug levels in VRs will also be performed. Many of these will be informed by findings from ASPIRE and will be fully explained in a Statistical Analysis Plan prior to the completion of follow-up in MTN-025.

10.8 Analysis of Secondary Endpoints

Primary analysis of the two main secondary endpoints, HIV seroconversion and acquisition of ARV-resistant HIV infection will be conducted similarly. We will calculate the incidence overall for each endpoint. Use of new and additional HIV-1 prevention technologies, such as oral PrEP and/or topical vaginal gels, will be captured on standardized data forms and will be taken into account in the analysis of HIV-1 incidence. We will calculate confidence intervals for incidence rates using the Poisson distribution. Although, statistical summaries will be provided, the results will likely have to be judged based on clinical and public health acceptability. Additional analyses will likely evolve based on results from ASPIRE. These will be outlined in the Statistical Analysis Plan prior to the end of study follow-up.

10.9 Missing Data

We are targeting a retention rate of 95% over the study period. Based on previous HIV Prevention Trials Network (HPTN) and MTN trials, we expect to have minimal missing data. In any situation with missing data, we will do appropriate secondary analyses that adjust for variables that may be related to the missingness mechanism. If missing data rates are higher than anticipated (over 10%), we will include covariates that are related to missingness in likelihood-based regression models. We will also perform sensitivity analyses to assess the potential impact of the missing data. These analyses will include imputing the data under the most extreme scenarios of information missingness, such as assuming everyone missing has an extreme value of the missing variable, and less informative imputation approaches.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study 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. Study CRF data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system.

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

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocpolicy.pdf) and the relevant appendix regarding source documentation (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocappndx.pdf).

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, for the investigational product tested, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval 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.

Audio files will be transcribed and immediately destroyed following a transcription quality assurance check. The site IoR or designee will be responsible for ensuring that these files have been destroyed.

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdfhttp://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdf).

12 CLINICAL SITE MONITORING

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

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including CFR Title 45 Part 46 and Title 21 Parts 50, 56, and 312
- Perform source document verification to ensure the accuracy and completeness of study data
- Verify proper collection and storage of biological specimens
- Verify proper storage, dispensing, and accountability of investigational study products
- Assess implementation and documentation of internal site quality management procedures
- Verify that current license/certification is available on site for study staff listed on the current FDA Form 1572, DAIDS IoRs, and Delegation of Responsibilities Log/Form.

The IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of certain study procedures. The IoR/designee will also allow inspection of all study-related documentation by authorized representatives of the MTN LOC, SDMC, and LC; NIAID, FDA, IPM, OHRP and local and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Boards/Ethics Committees

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 will have obtained IRB/EC approval and the protocol will have been submitted to the FDA. The IoR will permit audits by the NIH, IPM, the FDA, OHRP, or any of their appointed agents.

13.2 Protocol Registration

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

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

Upon receiving final IRB/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 will be forwarded to DAIDS for cross-referencing with other INDs for the study product. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement executed by NIAID and IPM.

Study implementation will also be guided by a common study-specific procedures manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study product and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN LOC, SDMC, LC and other designated members of the Protocol Team.

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

13.4 Risk Benefit Statement

13.4.1 Risks

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

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

Participants at sites requiring partner notification in response to diagnosed STI or HIV infection could have problems in their relationships with their sexual partners. It is possible that the participant and her partner may feel the ring during sexual activity. Participants also could experience problems associated with use of study product in their partner relationships.

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

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

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

Please note: Study product risks will be updated when the safety and effectiveness data from ASPIRE are available.

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

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

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

13.4.2 Benefits

MTN-025 (HOPE) will only be implemented if the dapivirine vaginal ring as tested in MTN-020 (ASPIRE) is found to be safe and effective, therefore, participants in the HOPE study will experience the direct benefit of using a product that has been found to be safe and effective in preventing HIV acquisition and will be considered for potential regulatory approval. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help to understand issues important for broader implementation of the dapivirine ring and/or for the development of other safe and effective interventions to prevent HIV acquisition. Participants may also 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 will be provided STI treatment in accordance with WHO guidelines free of charge. In addition, STI testing, counseling and treatment, as well as HIV testing and counseling will be available for participants' partners. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals.

13.5 Informed Consent Process

Each study participant will provide written informed consent prior to both screening and enrollment. Written informed consent will also be obtained for long-term specimen storage and possible future testing, for off-site clinic visits as needed, as well as for participation in the 'Decliner Population'. Neither consent for long-term specimen storage nor off-site study visits are required for study participation. Further, participation in the 'Decliner Population' does not preclude MTN-025 full study participation in the future. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://rsc.tech-res.com/policiesandregulations/). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

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

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

- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The real benefit of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time
- New information, including results of MTN-020 (ASPIRE) and IPM 027 (The Ring Study), and information about other effective HIV-prevention products will be provided to MTN-025 (HOPE) participants.

13.6 Participant Confidentiality

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

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored securely. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' identification numbers to identifying information will be stored in a locked file in an area with limited access. All digital audio files will be stored on password-protected computers. Audio files will be transcribed. Please see SSP for guidance regarding audio file destruction. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

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

13.7 Special Populations

13.7.1 Pregnant Women

Women who test positive for pregnancy at Screening or Enrollment Visits will not be eligible to participate in this study. Should a woman test positive for pregnancy after Enrollment, a product hold will be implemented but all follow-up visits will be completed and data collected per Section 7.6.2. A urine pregnancy test will be performed at scheduled study visits, and additionally at interim visits as indicated; the IoR/designee will temporarily discontinue study product for participants who test positive for pregnancy. During the informed consent process, women will be informed that the VR is not a method of contraception and the effects of the VR on a developing human fetus are unknown.

Animal studies have failed to demonstrate risk to the fetus, but there are no adequate and well-controlled studies in pregnant women completed to support their inclusion to date.

13.7.2 Children

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

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 and time away from work. Site-specific reimbursement amounts will be specified in the study informed consent forms. Each study site will determine appropriate compensation with their overseeing IRB/EC.

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 III. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will provide information regarding the known efficacy of the study product 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-Infected

Care for participants identified as HIV-infected is described in Section 9.6.

13.11 Study Discontinuation

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

14 PUBLICATION POLICY

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

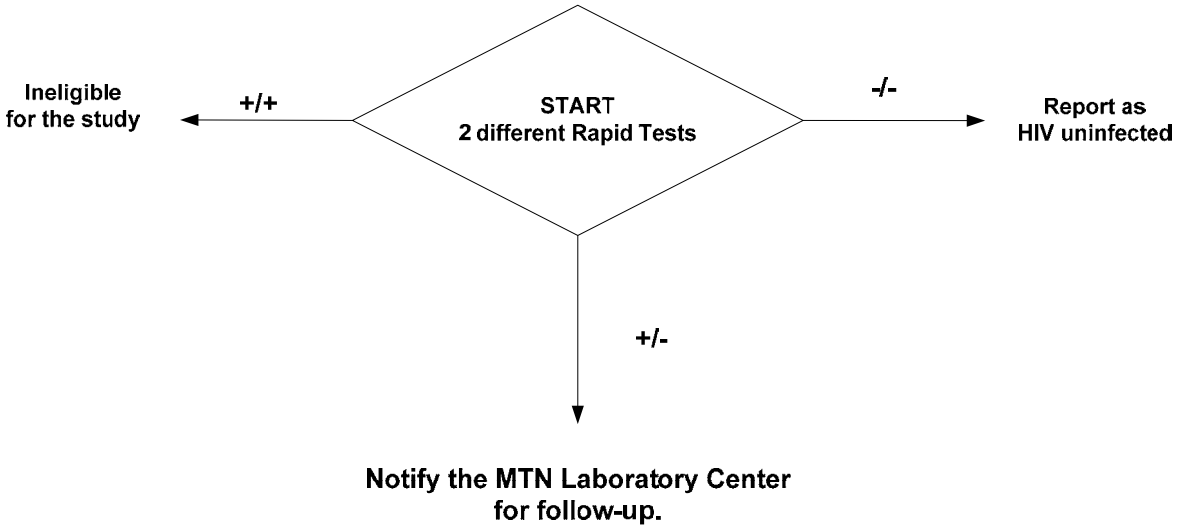
15 APPENDICES

Appendix I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

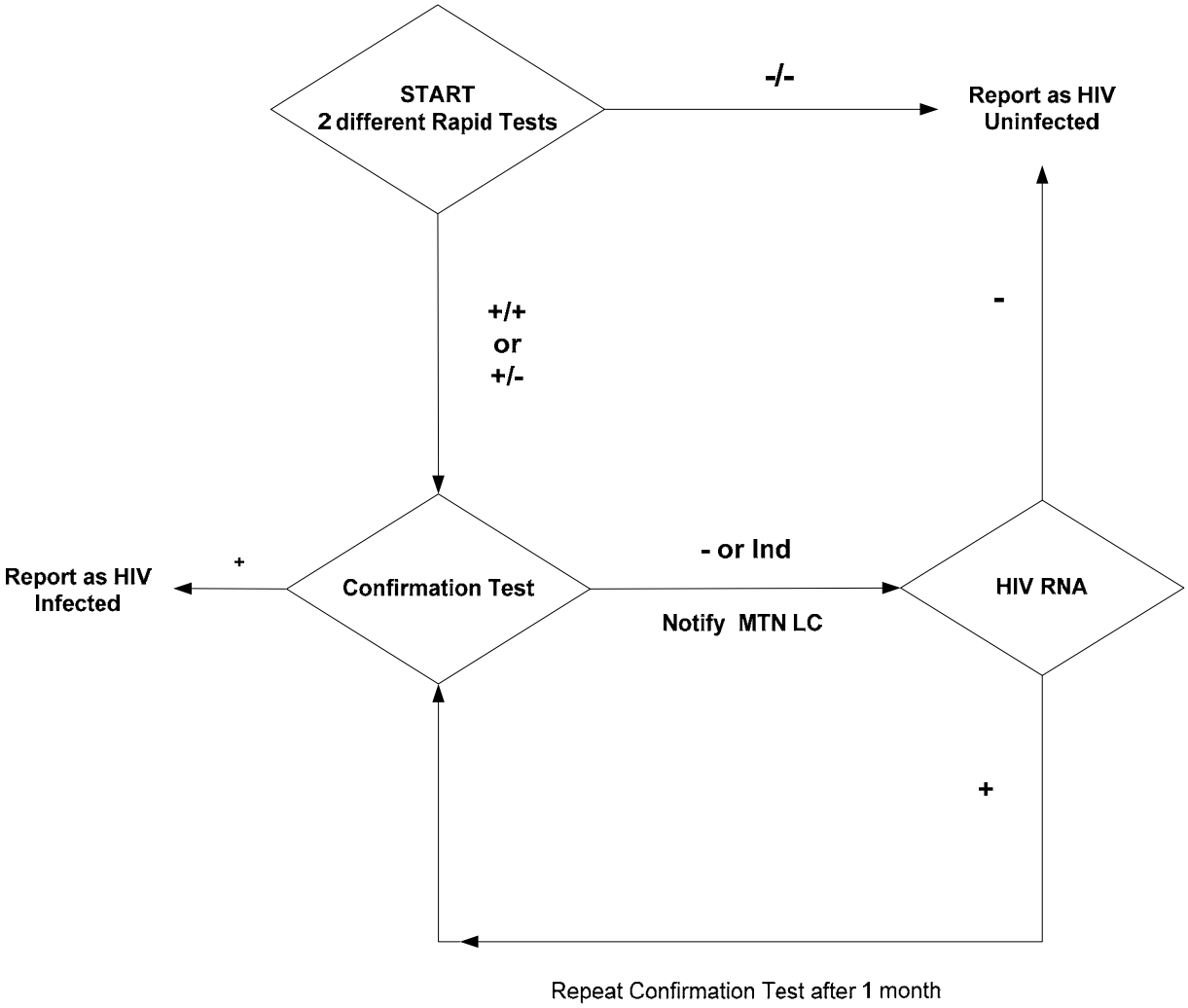
				Study Months			
		SCR	ENR	M. 1 and 2.	Quarterly Visits	PUEV	Study Exit/ Term. Visit (~ 1 Month after the PUEV)
ADMINISTRATIVE AND REGULATORY							
Obtain informed consent		X	X				
Assign a unique Participant Identification (PTID) number		X					
Assess and/or confirm eligibility		X	X				
Collect/review/update locator information		X	X	X	X	X	X
Provide reimbursement for study visit		X	X	X	X	X	X
Schedule next visit		*	*	X	X	X	*
BEHAVIORAL							
Contraceptive counseling		X	X	X	X	X	*
HIV/STI risk reduction counseling		X	X	X	X	X	X
HIV pre- and post-test counseling		X	X	X	X	X	X
Protocol adherence			X	X	X		
Conduct a behavioral assessment			X		X	X	X
Conduct social harms assessment					X	X	
CLINICAL							
Obtain/update medical and menstrual history		X	X	X	X	X	X
Obtain/update concomitant medications		X	X	*	X	X	X
Conduct a physical examination		X	*	*	*	X	*
Perform a pelvic examination		X	*	*	*	X	*
Offer contraceptives		*	*	*	*	*	*
Disclose available test results			X	X	X	X	X
Record/update AEs				X	X	X	X
Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings		*	*	*	*	*	*
LABORATORY							
URINE	hCG	X	X	X	X	X	X
	Urine culture	*ǂ	*ǂ	*ǂ	*ǂ	*ǂ	*ǂ
	NAAT for GC/CT	X	*	*	*	X	*
BLOOD	HIV-1 serology	X	X	X	X	X	X
	CBC with platelets	X				X	
	Chemistries	X		*	*	X	
	Syphilis serology	X		*	*	X	
	Plasma sample for DPV testing and archive		◊		X	X	X
PELVIC	Rapid test for Trichomonas	X	*	*	*	X	*
	Vaginal fluid (self-collected)		X	X	X	X	X
	Pap Smear interpretation	*					
	Adherence assessment(s): Returned Study VR			X	X	X	
STUDY PRODUCT/ SUPPLIES							
Offer condoms		X	X	X	X	X	X
Provision of study VR use instructions			X	*	*		
Provision of study VR			X	X	X		
Removal and collection of used/unused study VR				X	X	X	
Digital exam(s) by clinician to check VR placement			*	*	*		

*X mandatory, *If indicated, ǂPer local standard of care*

APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING-SCREENING/ENROLLMENT



APPENDIX III: ALGORITHM FOR HIV ANTIBODY TESTING FOR FOLLOW-UP



Ind: Indeterminate test results
LC: Laboratory Center

APPENDIX IV: SAMPLE INFORMED CONSENT DOCUMENT (SCREENING)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NICHD, NIMH, NIH

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

HIV Open-label Prevention Extension (HOPE)

Version 2.0
December 16, 2014

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

INFORMED CONSENT
This is a screening consent form. You are being asked to volunteer for screening tests to find out if you are eligible for a research study MTN-025, otherwise known as the **HIV Open-label Prevention Extension (HOPE)** trial. The research study you participated in, MTN-020: ASPIRE, *A Study to Prevent Infection with a Ring for Extended Use*, showed that the dapivirine vaginal ring can reduce the chances of HIV-uninfected women from getting the HIV virus by [SITES TO INSERT: from X to X percent]. The study also learned that the dapivirine vaginal ring is [SITES TO INSERT: *safe (meaning that they do not produce significant health problems in persons who take them)*] when used by HIV-uninfected women. Only through the participation of volunteers in clinical research can the safety and effectiveness of medicine be better understood. More data is needed on the safety of the dapivirine vaginal ring. Because you took part in the ASPIRE study, you are being offered the opportunity to use the safe and effective dapivirine vaginal ring as part of this new study. A total of 2629 women enrolled into MTN-020 (ASPIRE) and all former ASPIRE participants who are eligible for MTN-025 (HOPE) may take part. It is anticipated that approximately 1000 to 2500 former ASPIRE participants will enroll in HOPE.

This Microbicide Trials Network (MTN) study is funded by the US National Institutes of Health (NIH) and is being conducted across multiple countries across Africa. The International Partnership for Microbicides (IPM) supplies the study product.

[INSERT NAME OF PRINCIPAL INVESTIGATOR] is in charge of this study at this clinic. Before you decide if you want to screen for this study, we want you to learn more about the trial. Screening examinations and tests, which include interview questions, urine, and blood tests, a physical examination and an examinations of your vagina, will be performed to better understand your health. The study staff will explain the exams and tests to you and what is expected of you. Once you understand the screening tests, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

YOUR PARTICIPATION IS VOLUNTARY
It is important that you know the following:

- You are only being asked to have the screening tests at this time. Even if you agree to have the screening tests, you do not have to join this study.
- Your participation is voluntary; you do not have to have the screening tests if you do not want to participate in this study.
- You may decide not to have the screening tests, or to withdraw from the screening tests at any time, without losing your regular medical care.
- You will receive the results of the screening tests even if you are not eligible to join this study.
- Some people may not be able to join this study because of information found during the screening tests. You are asked to tell the study staff about any other studies you are taking part in, or thinking about taking part in. This is very important for your safety.
- If new information is learned about the study, or the study product, you will be told about this as soon as possible.

PURPOSE OF THE SCREENING TESTS AND THE STUDY
The main purpose of these screening exams and tests is to find out if you can join this research study. This research study will test if a vaginal ring containing the medicine dapivirine is used as directed and found to be safe in participants who attend clinic visits. Women will be in this study for approximately 13 months depending upon when they enroll in the study; however this period could be shorter or longer than anticipated. You will be notified if the study extends beyond 13 months.

STUDY PRODUCT
There is one kind of vaginal ring that will be used in this study, a ring containing dapivirine. Unlike ASPIRE, there is no placebo vaginal ring (a ring without the study medicine) in HOPE, so all HOPE participants will receive a vaginal ring containing dapivirine. This ring is the same dapivirine vaginal ring used in ASPIRE. Dapivirine vaginal rings have been previously tested and found to be generally safe, well-tolerated and effective in HIV prevention in women. HIV is the virus that causes AIDS. The medicines that are being tested by researchers to prevent HIV infection work in different ways. Dapivirine works by preventing HIV from making copies of itself, thereby stopping the spread of HIV in the body.

WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN THE SCREENING EXAMS AND TESTS?
If you agree to have screening tests, they can be done today. Ideally, all procedures will be completed today. However if you have to come back to complete this visit, some procedures may need to be repeated.

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

- You will be asked questions about:
  - Where you live
  - Your medical health, what medications you are taking, and menstrual history

- Other questions to ensure you are eligible for this study, and to make sure that you understand the study requirements.

- Study staff will:
  - Perform a physical examination
  - Talk with you about the requirements of the study including using an effective method of contraception throughout your participation in this study
  - Test your urine for:
    - Infections passed through sex
    - Pregnancy
      - If you are pregnant you cannot join this study because the risks to your baby are unknown.
      - If the study is still open after your pregnancy, you may come back here to find out if you are eligible.
      - If you are not pregnant, you will be told about ways to avoid becoming pregnant, such as the use of contraception.

  - Take a blood sample [Sites to insert amount]:
    - To test the health of your blood, liver and kidneys
    - To test for infections passed through sex, including HIV
      - You will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we know your results for sure. You must receive your HIV test results to be in this study. If the test shows you have HIV, you cannot join this study. We will tell you where you can get care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.

  - Perform a pelvic examination:
    - The study doctor or nurse will use a speculum, a plastic or metal instrument used to separate the walls of the vagina. The study doctor or nurse will look at your vagina and cervix for signs of infection, and other problems. Your cervix is located at the top of the vagina and it forms the lower end of the womb (uterus). They may also take some fluids to test for other possible problems if they feel it is necessary.
    - The study staff <u>may</u> also collect samples from your cervix for testing, including a "Pap test". If the test shows a problem, it could mean you should have more tests. If you have a written report confirming that you had a normal Pap test in the past 12 months or if you had an abnormal Pap test but had follow-up and a written report indicating no treatment was required, you will not need to have a Pap test during this visit.

  - Give you treatment or refer you for treatment for infections passed through sex, if needed.
  - Tell you about other services if you need them
  - Offer you condoms. Condoms are highly effective in preventing the sexual transmission of HIV and reducing the risk for other sexually transmitted diseases

(STDs). Study staff can provide you with condoms along with additional information about other ways to avoid getting HIV infection.
- Schedule your next visit to enroll in MTN-025, if you are eligible and willing

The study staff will review your test results with you when they are available. If the results show you can join the MTN-025 study, the study staff will explain the study to you and answer any questions you have. If you decide to be in this study, you will be asked to sign another consent form.

RISKS AND/OR DISCOMFORTS

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

Risks of 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 usually stops shortly after the examination.

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

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

BENEFITS

The primary benefit to joining this study is having access to a product that has been shown to be safe and effective in preventing HIV. If this screening visit shows you are eligible to participate, an enrollment visit will be scheduled.

You will have a physical examination, pelvic examination, and tests to check on the health of your blood, liver, and kidneys. If these tests show that you might have health problems, you will be told where to get medical care and other services available to you.

You will be counseled and tested for infections passed through sex. If you have these infections, you may be offered treatment for them, if needed. If you are infected with HIV, you will be told about medical care, counseling, and other available services that could be of help to you. For other health problems that cannot be treated at this clinic, the study staff will refer you to other places where you may receive medical care. If your Pap test result shows anything that is not normal, you will be referred for advice and/or treatment.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SCREENING TESTS WITHOUT YOUR CONSENT
You may be withdrawn from the screening tests without your consent if:

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

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

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

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

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH
- [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- IPM, the organization that supplies the study 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

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

The researchers will do everything they can to protect your privacy.

RESEARCH-RELATED INJURY

[Sites to modify with their site-specific research-related injury institutional policy:] It is unlikely that you will be injured as a result of having the screening tests. 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 or your insurance company will be charged for this treatment. You do not give up any legal rights by signing this consent form.

CLINICALTRIALS.GOV

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

PROBLEMS OR QUESTIONS

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

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

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

SIGNATURES

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

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

APPENDIX V: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NICHD, NIMH, NIH

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

HIV Open-label Prevention Extension (HOPE)

Version 2.0

December 16, 2014

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

INFORMED CONSENT
You are being asked to take part in the **MTN-025 HIV Open-label Prevention Extension (HOPE)** trial. The research study you participated in, MTN-020: ASPIRE, *A Study to Prevent Infection with a Ring for Extended Use*, showed that the dapivirine vaginal ring can reduce HIV-uninfected women's chances of getting the HIV virus by [SITES TO INSERT: from X to X percent]. The study also learned that the dapivirine vaginal ring is [SITES TO INSERT: *safe (meaning that it does not cause significant health problems)*] when used by HIV-uninfected women. More data is needed on the safety of the dapivirine vaginal ring. Because you took part in the ASPIRE study, you are being offered the opportunity to use the safe and effective dapivirine vaginal ring as part of this new study. A total of 2629 women enrolled into MTN-020 (ASPIRE) and all former ASPIRE participants who are eligible for MTN-025 (HOPE) may take part. It is anticipated that approximately 1000 to 2500 former ASPIRE participants will enroll in HOPE.

This Microbicide Trials Network (MTN) study is funded by the US National Institutes of Health (NIH) and is being conducted across multiple countries across Africa. The International Partnership for Microbicides (IPM) supplies the study product.

[INSERT NAME OF PRINCIPAL INVESTIGATOR] is in charge of this study at this clinic site.

YOUR PARTICIPATION IS VOLUNTARY
Before you decide if you want to join this study, we want you to learn about the study. The study staff will talk with you about the study and answer your questions. Once you read, discuss, and understand the study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep. You may decide not to join or to withdraw from the study at any time.

PURPOSE OF THE STUDY

This research study will test if a vaginal ring containing the medicine dapivirine is used as directed and found to be safe in participants who attend clinic visits. Women will be in this study for approximately 13 months depending upon when they enroll in the study; however the duration of study participation could be shorter or longer than anticipated. You will be notified if the study extends beyond 13 months.

STUDY PRODUCT

There is one kind of vaginal ring that will be used in this study, a vaginal ring containing dapivirine. Unlike ASPIRE, there is no placebo vaginal ring (a ring without the study medicine) in HOPE, so all HOPE participants will receive a vaginal ring containing dapivirine. This ring is the same dapivirine vaginal ring used in ASPIRE. Dapivirine vaginal rings have been previously tested and found to be generally safe, well-tolerated and effective in HIV prevention in women. This study is testing whether a vaginal ring containing dapivirine can help to prevent the spread of HIV. HIV is the virus that causes AIDS. The medicine that is being tested to prevent HIV infection works in different ways. Dapivirine works by preventing HIV from making copies of itself, thereby stopping the spread of HIV in the body.

The staff can provide you additional information about other ways to avoid getting HIV infection. The most effective way to protect against getting HIV infection during sex is to use a condom every time you have sex.

WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN THE MTN-025 STUDY?

If you decide to enroll in the study, you will have a clinic visit today and monthly for the next three months, then quarterly thereafter. You will insert a new vaginal ring monthly for approximately 12 months. For some participants, this period of time may be less, study staff will provide you with an estimate of how long you will use the ring. You will have a final study visit to check on your health approximately 4 weeks after the final ring is removed. Study visits may be required beyond the final study visit to monitor your health. Visits will take approximately *[site to insert required length of time].*

You will be asked to:

- Confirm you are able to join the study and that you understand the study requirements
- Answer questions about your vaginal practices, including sexual activity
- Provide updated information about where you live and how we can contact you
- Describe any changes in your health, what medicines you are taking, and your menstrual periods
- Describe any health problems you have had since your last visit, including problems with the study ring

You will be asked to use a study vaginal ring. As part of using this ring you will:

- Talk with study staff about how to properly wear and use the study ring
- Receive new study rings (monthly or every three months) and insert a new study ring (monthly). If you are inserting a new ring at a clinic visit, and you are having difficulty a study clinician may help you
- If needed, have an examination performed to ensure the ring is properly inserted.
- Return your vaginal ring(s) to study staff. Study researchers will keep these rings and run additional tests on them. These tests will help researchers better understand your ring use.

- Be able to return to the clinic to have the ring reinserted if the ring falls out and you are uncomfortable reinserting it yourself

You will be asked to answer questions about:

- Your experience using the vaginal ring, including whether or not the ring was removed from or fell out of your vagina.
- Any problems you may have had during your participation in this study.
- Vaginal practices that may affect how the study drug is absorbed by your body.
- Things that may make you uncomfortable, such as questions about drug use. You may use a computer to answer these questions or a staff member may ask you these questions. It is important that you know that you will answer these questions in private and your responses will be kept confidential.

You will have the following clinical procedures performed:

- A physical examination
- Provide a sample of blood [insert amount] to:
    - Check the health of your blood, liver and kidneys
    - Test for HIV. You will be told your HIV test results as soon as they are available. 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 clearly positive, but also not clearly negative. In that case, we will do more tests until we know your results for sure. You must receive your HIV test results to be in the study. If the test shows you have HIV, you cannot join the study. We will 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.
    - Additional testing may be performed as part of quality control.
    - See how much of the study product is being absorbed by your body and how it affects your body.
- Provide a urine sample to:
    - Check to see if you are pregnant
    - Test for infections passed through sex
- Provide vaginal fluid and cervical fluid samples:
    - To see how the dapivirine vaginal ring protects against HIV and to explore the health of the female genital tract. The vaginal fluid and cervical fluid collected will be used for research purposes only.
- A pelvic examination when the vaginal ring is removed for the final time. The study doctor or nurse will use a speculum. A speculum is a plastic or metal instrument used to separate the walls of the vagina. It is used so the doctor or nurse can examine the vagina and the cervix during the examination. Your cervix is located at the top of the vagina and it forms the lower end of the womb (uterus). They will check for signs of infection, and other problems. They may also take some fluids to test for STIs and other possible problems if they feel it is necessary

As part of the clinical procedures you will:

- Receive the results of your tests when available
- Learn about other services available to you
- Receive treatment or be referred for treatment for problems that the study staff may find.
- Receive counseling. You will discuss:
    - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to prevent HIV and other infections passed through sex
    - The rules of the study and how to follow the rules
    - Contraception and ways to prevent getting pregnant
- Be offered condoms. Condoms are highly effective in preventing the sexual transmission of HIV and reducing the risk of other sexually transmitted diseases (STDs). Study staff can provide you with condoms along with additional information about other ways to avoid getting HIV infection.
- You will schedule your next visit

If you leave the study early, you will be asked to complete a final clinic visit and evaluations. Various procedures will be completed at this visit, including a pregnancy and HIV test.

It may be necessary for additional visit(s) and procedures in the event of unforeseen or unanticipated results; difficulties in sample shipping, processing, or testing; and/or if you are experiencing any symptoms or changes in your physical condition. For example, at any time during the study, vaginal and/or cervical swabs, blood samples and urine may need to be collected if you are having symptoms or if you are suspected to have an infection.

Interim/Unscheduled Visits

Study staff will discuss with you the importance of contacting the clinic as soon as you notice changes in your physical condition or when you experience health related issues. It may be necessary to come to the clinic for an unscheduled visit. Also, it is possible that you may be asked to come to the clinic for an unscheduled visit in the event of an abnormal test result; difficulties in sample shipping, processing, or testing; or for other reasons.

In-depth Interview(s) and Group Discussions

You <u>may</u> be asked to participate in interview(s) with a trained staff member or you <u>may</u> be asked to participate in a group discussion with other study participants about opinions that you or other participants have. If you are asked to participate in these study activities, you will be compensated for your time and effort.

If you are asked to participate in a group discussion, you will be asked to discuss your use of the study product, your feelings about the study product and trial participation, your vaginal practices and other questions that can help researchers to better understand participants' experiences while taking part in the study. These discussions will last about one hour.

If you are asked to participate in an interview, you will be asked questions about your use of the ring, your preferences and opinions, your experiences with using the ring during sex, and any problems you may have had using the ring. The interviews will be audio-recorded to make sure to record your words exactly how you said them. The voice recordings will be destroyed as soon as the audio recording has been typed and checked. The audio recording, notes, and

analyses from these materials will be kept confidential and will only use study numbers or fake names. This means that no one other than the MTN-025 (HOPE) study team will have access to your responses. The information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-025(HOPE) study team for the purposes of this research.

If you become infected with HIV
Your participation in this study will not cause HIV infection. However, there is always a chance that through sexual activity or other activities you may become HIV-positive. If the HIV tests confirm that you have been infected with HIV, you will stop using the ring, but we will ask you to continue to come into the clinic for regularly scheduled visits for some of the study procedures. You will have more blood tests at different time points after your HIV infection is discovered to find out which drugs would be inappropriate for your type of HIV-1 (HIV drug resistance), the amount of immune protection in your blood (CD4+ T-cell count), and the amount of HIV in your blood (viral load). You may be referred to other research studies. If you join another study it may not be necessary to collect additional blood for testing. In the event you become HIV-positive, study staff will counsel and refer you for medical care and other available services while you are in this study.

It may be necessary, depending upon local and national health requirements, for study staff to report diseases, including HIV, identified among MTN-020 (ASPIRE) study participants. The reportable diseases at this site are [Sites to insert].

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 examination.

Risks of Study Rings
The study rings can cause some side effects, such as an allergic reaction. Signs of an allergic reaction include, but are not limited to: Rash or other skin irritation, itching, joint pain, or difficulty in breathing. We do not yet know all the side effects of the rings. Some, but not all women who used the 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. 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 symptoms associated with toxic shock syndrome, i.e., sudden high fever, a faint feeling, diarrhea, headache, a rash, and muscle aches.

Finally, it is also possible that you or your partner may feel the ring during sexual activity. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

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

Other Possible Risks
If you become infected with HIV and continue to use the ring it is possible that you may develop HIV drug resistance. This means that any virus that is drug resistant will survive and continue to reproduce (make copies of new HIV) in the presence of the drug that normally weakens or kills it. HIV drug resistance could make it difficult to use dapivirine or drugs like it to treat the HIV. Drug resistance only occurs if you were to become infected with HIV and continue to use the study product.

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

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

If you are chosen to participate in the group discussion, other participants will hear what you say. We will not reveal your full name to other participants. We will also ask every participant not to tell anyone outside of the group what any person said during the discussion. While it is not at all likely that your discussion will be made public, we cannot guarantee that everyone will keep the discussion private.

BENEFITS

[SITES TO UPDATE: Participants in the MTN-025 (HOPE) trial will experience the direct benefit of using a vaginal ring that has been found to be safe and efficacious in preventing HIV transmission.]

In addition, you will have physical examinations, pelvic examinations, and tests to check on the health of your blood, liver, and kidneys. If these tests show that you might have health problems, you will be told where to get medical care and other services available to you.

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

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

PREGNANCY AND BREASTFEEDING

The dapivirine ring is not birth control. You must agree to use an effective method of birth control such as an intrauterine contraceptive device (IUCD), birth control pills or other hormonal-based method (except for vaginal rings), unless you underwent a medical procedure to permanently be unable to become pregnant, i.e., sterilization.

We do not know if the dapivirine ring has any effect on pregnancy, on the fetuses of a women who use the vaginal ring while pregnant, or on the babies of women who use the ring while breastfeeding. Because of this, pregnant and breastfeeding women may not join this study. You may be able to start using the vaginal ring after your pregnancy, provided that you are not breastfeeding. The study staff will talk more with you about this after your pregnancy. Women who join the study must agree to use effective contraception 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 or your baby may need. The study does not pay for this care. You will stop using the ring, but we may ask you to keep coming here for study visits as originally planned. We will change the study procedures as needed to protect your health while you are pregnant. *[Sites to include/amend the following:* We may also contact you to find out about the health of your pregnancy, and the health of your baby up to one year old, if you have a baby. We may also contact you about a study that collects information about pregnancy and babies up to one year old.] The outcome of your pregnancy is important to study staff; therefore your pregnancy will be followed until the results of your pregnancy are known.

NEW INFORMATION

You will be told about new information from this or other studies that may affect your welfare or willingness to stay in this study. It is important you know that the study product, the dapivirine ring, is among the most advanced HIV prevention products that can be offered to you [SITES TO INSERT MTN-020 DATA HERE]. In addition to being tested as part of the ASPIRE trial, the

ring was also tested in IPM 027. IPM 027 results will be provided to participants when they become available. In the future, vaginal rings containing more than one type of medicine may become available. If a new product like this were to become available, it could be more protective than the ring tested as part of MTN-020 (ASPIRE) and IPM 027 (The Ring Study), leading to fewer HIV infections, however, no other vaginal ring has been found to work at this time.

It is also important for you to know that other drugs are being tested for HIV prevention. The HIV prevention researchers working on this MTN-025 (HOPE) are committed to sharing any data with you that becomes available, regardless of the product, if it is found to be effective in preventing the transmission of HIV. You will also be told when study results may be available, and how to learn about them.

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

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

- The study is cancelled by the US FDA, US NIH, International Partnership for Microbicides, the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/ the Ethics Committee (EC). An IRB/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
- A study doctor decides that using the vaginal ring would be harmful to you
- You require a treatment that you may not take while using the study vaginal ring
- You have a bad reaction to the study vaginal ring

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

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

ALTERNATIVES TO PARTICIPATION

[*Sites to include/amend the following:]* There are no gels, tablets or vaginal rings currently available in this country to protect against HIV during sex. Consistent use of condoms is the only available known way to protect against HIV during sex. 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 contraception. 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 may receive [*Sites to insert amount $xx*] for any visits which occur in between your normally scheduled visits.

CONFIDENTIALITY

Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff may use your personal information to verify that you are not in any other research studies. [Sites to insert information about systems currently in place to ensure participants are not part of other conflicting studies, including biometric identification systems.] 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
- [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- IPM, the organization that supplies the study 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

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

The researchers will do everything they can to protect your privacy.

RESEARCH-RELATED INJURY

[Sites to modify with their site-specific research-related injury 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 or your insurance company will be charged for this treatment. You do not give up any legal rights by signing this consent form.

CLINICALTRIALS.GOV

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

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

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

PROBLEMS OR QUESTIONS

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

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

SIGNATURES

[Sites to insert signature/initial blocks as required by the local IRB/EC:]

[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

There might be a small amount of blood, vaginal fluid and cervical fluid samples left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your leftover blood, vaginal fluid, and cervical fluid samples, and related health information for use in future studies. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range. If you agree, your samples and related health data will be stored safely and securely at facilities that are designed so that only approved researchers will have access to the samples. Some of these research facilities may be outside of your country. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. You can still enroll in this study if you decide not to have leftover blood, vaginal fluid and cervical fluid samples stored for future studies. If you do not want the left-over blood, vaginal fluid and cervical fluid samples stored, we will destroy these left over specimens. Any future studies that may be done will also have to be approved by an Ethics Committee/ Institutional Review Board. 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.

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

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

CONSENT FOR OFF-SITE VISITS

[Sites to modify as needed]

Members of the research team at this clinic may be able to schedule off site visits with you at your home or at another location as part of the study. If needed, and, if you agree, some of the scheduled study visits and some of the study procedures may take place at your home or other location outside of the research clinic, if you are unable to come into the clinic. If, for example, you need to receive a new ring or to have a urine or blood sample collected, study staff could come to you your home or meet you at another location, if you give your permission and if the study staff determine that it is appropriate. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the time it will take) and the procedures in-place to maintain your information in a confidential manner. However it is important that you know that off-site visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

In order to conduct visits outside of the clinic, we will need you to give us permission to do so. Please read carefully the following statement and initial and date one option. Choosing not to be visited outside of the study clinic will not affect your participation in this study. Even if you agree today, you can withdraw your consent for off-site visits at any time by providing your request in writing to the person in charge of this study. In addition, before each off-site visit, we will confirm with you that you still agree and remember today's discussion.

_____ I DO agree to be visited at a location other than the study clinic by clinic staff, when necessary

Initials and Date

_____ I DO NOT agree to be visited at a location other than the study clinic by clinic staff, when necessary

Initials and Date

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to participate in this study, please sign your name or make your mark below.

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

APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT (MTN-025 DECLINER POPULATION) MTN-025

SAMPLE INFORMED CONSENT FORM- Screening and Enrollment MTN-025 Decliner Population

DIVISION OF AIDS, NIAID, NIH, NIMH, NICHD

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

Version 2.0
December 16, 2014

PRINCIPAL INVESTIGATOR:
PHONE:

INFORMED CONSENT
You are being asked to take part in this research study because you are a woman who took part in the MTN-020 (ASPIRE) trial and have decided to delay, decline to take part in the MTN-025 (HOPE) trial. Other women like you will participate in this study across multiple sites. Before you decide if you want to join this study, we want you to know about the study. This Screening/Enrollment consent form gives you information about this study. MTN-025 (HOPE) staff will talk with you about the study and answer any questions you may have.

This Microbicide Trials Network (MTN) study is funded by the US National Institutes of Health (NIH) and is being conducted across multiple countries across Africa. A total of 2629 women enrolled into MTN-020: ASPIRE and all former participants who are eligible may take part in the MTN-025 or in the MTN-025: Decliner Population.

YOUR PARTICIPATION IS VOLUNTARY
Participation in this study is voluntary. You will be asked to sign or make your mark on this form to indicate whether you agree to participate in this study. Before you decide whether to be in MTN-025 Decliner Population, we would like to explain the purpose of the study. If you decide to enroll in this study, you may decide to withdraw from the study at any time. There will be no penalty for refusing to participate or choosing to withdraw from this study.

It is important that you know that if you change your mind and wish to take part in the MTN-025 trial, you can enroll, provided that the study is ongoing and that you are eligible.

PURPOSE OF THE DECLINER POPULATION
The main goal of the Decliner Population is to better understand MTN-020 (ASPIRE) participants' reasons for refusal to take part in the MTN-025 (HOPE) trial. MTN-025, is a study that provides former ASPIRE participants with access to the dapivirine vaginal ring, a product that has been shown to reduce the chances of women from getting the HIV virus by [To be updated: X to X percent]. The study also learned that the dapivirine vaginal ring is [To be

updated: *safe (meaning that it does not produce significant health problems in persons who take it)*].

STUDY PROCEDURES

It is expected that the procedures involved with the MTN-025 Decliner Population will be completed in one visit. If you agree to join this study, you will be asked to answer questions about your behavior(s) and you also may be asked to complete an in-depth interview (IDI) in the presence of one or two MTN-025 (HOPE) research staff members. If you agree to take part in this study, the interviewer will ask you some brief questions and write your responses on a form. Multiple visits may be needed to complete the IDI and questionnaire(s). During the IDI, the interviewer will also ask in-depth questions, during which time notes may be taken and the conversation will be audio-recorded.

You will be asked some general questions, such as your age, education, living situation, relationship status and health. You will also be asked about other clinical trials or HIV-related studies that you may be currently participating in. The interviewer will also ask questions about your experiences while participating in the ASPIRE trial. These will include questions about different ways women used their study product, their sexual practices, as well as your use of the study product and your sexual practices.

We expect the interview will take approximately 2 hours. The IDI it will be completed at a place agreed upon by you and the study staff, which may be your home, a designated neutral study interview location, the clinic you went to for your ASPIRE visits or another convenient place of your choice.

The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or fake names. The information that links you to the research data will be kept in a secure location that will be accessed only by members of the HOPE study team for the purposes of this research.

To obtain information about your participation in ASPIRE, the HOPE study team may need to access your ASPIRE research records. By signing this form, you are giving the HOPE study team permission to look up and record the needed information from your research record.

RISKS AND/OR DISCOMFORTS

During the interview we may ask you some questions that cause you to feel embarrassed or uncomfortable. You can choose not to answer questions in the interview at any time. It is also possible that people or family members may find out you are participating in this study. As a result, they may ask questions about the study, treat you unfairly, or you may encounter problems in being accepted by your family and/or community.

Another possible risk of this study is loss of confidentiality of the information you give. Every effort will be made to protect your confidential information, but this cannot be guaranteed. To reduce this risk, we will strictly protect the information recorded during your interview. The audio recording, notes, and analyses from these materials will be kept confidential. This means that no one other than the HOPE interview team will have access to your responses. The information that links you to the research materials will be kept in a secure location. Your audio recordings will also be kept in a secure location and only people involved with the study will have access to these recordings. When the information on the audio recording is typed onto

paper and fully checked, the recording will be destroyed. Study leaders will make sure this happens.

NEW INFORMATION
You will be told about new information from this or other studies that may affect your welfare or willingness to stay in this study.

BENEFITS
There are no direct benefits to participating in this study. However, the information you provide may help researchers improve the design of future studies.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT
You may be removed from this study without your consent for the following reasons:

- The study is stopped or canceled
- The study staff feels that staying in the study would be harmful to you
- The study is stopped by NIH, the MTN, International Partnership for Microbicides (IPM), the Office for Human Research Protections (OHRP), other government or regulatory authorities, or site IRBs/ECs
- Other administrative reasons

ALTERNATIVES TO PARTICIPATION
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 we know about.

COSTS TO YOU
There is no cost to you for being in this study.

REIMBURSEMENT
[*Sites to modify/insert text as necessary for planned local reimbursement:*]
You will receive [$xx] for your time, effort, and travel.

CONFIDENTIALITY
We will do our best to make sure that the personal information gathered for this study is kept private. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

This Microbicide Trials Network (MTN) study is funded by the US NIH.

Your records may be reviewed by any or all of the following:

- The MTN-025 study staff
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- Site IRBs/ECs
- IPM
- Representatives of the US Federal Government, including the US FDA, US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH

PROBLEMS OR QUESTIONS
If you ever have any questions about this study, 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 telephone number and/or physical address of above].

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

[Sites to modify with their site-specific research-related injury based upon their institutional policy:
RESEARCH-RELATED INJURY
It is unlikely that you will be injured as a result of taking part in the MTN-025 Decliner Population. 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 or your insurance company will be charged for this treatment. You do not give up any legal rights by signing this consent form. *]*

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

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

Reference List

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SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

MTN-025

DAIDS Protocol #: 11985

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 2.0/ 16 December 2014

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-025 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. IRB approval is required before implementation of the modifications contained in this amendment. All IRB requirements must be followed.

Please file this Summary of Changes, Version 1.1 of the protocol and all associated IRB correspondence in your essential documents files for MTN-025.

Summary of Revisions

To ease in the review process, all revisions are displayed below. A summary of revisions is provided below:

1. The Protocol Team Roster has been updated.
2. In the Protocol Summary, updates were made to remove the randomization from the Study Design, to allow for an extension to follow-up, and to modify the visit schedule accordingly.
3. In Section 2, INTRODUCTION, background information is updated to incorporate updated information contained within the IB and to omit product-specific language or reference to ongoing MTN trials. Study Design is updated to remove the randomization.
4. In Section 3, STUDY OBJECTIVES, edits are made: to study objectives to prevent redundancy in data collection and analysis across protocols, and to coincide with the removal of randomization and the modified visit schedule.
5. In Section 4, STUDY DESIGN, minor edits are made: for clarity and consistency with the modified study objectives, removal of randomization and modified visit schedule.
6. In Section 5, STUDY POPULATION, eligibility criteria are clarified and the randomization language is removed.
7. In Section 6, STUDY PRODUCT, edits are made: for consistency with the removal of randomization and the modified visit schedule.
8. In Section 7, STUDY PROCEDURES, edits are made: for consistency with the removal of randomization and the modified visit schedule.

9. In Section 8, ASSESSMENT OF SAFETY, minor edits are made: for clarity and consistency with current policy and with the removal of randomization.
10. Section 10, STATISTICAL CONSIDERATIONS, language is modified to reflect the revised study objectives and endpoints, power estimates, oversight of the Interim Study Review (ISR) Committee, and planned data analysis resulting from the removal of randomization and from the modified visit schedule. Figure 2 was deleted.
11. Section 13, HUMAN SUBJECTS PROTECTION, is updated to reflect the current DAIDS Protocol Registration template language, the removal of randomization and the new risk language based upon the updated Dapivirine Vaginal Ring Investigator's Brochure.
12. Appendix I: Schedule of Study Visits is edited for clarity and consistency with the modified study procedures, removal of randomization and modified visit schedule.
13. The sample informed consent documents have been updated to reflect modified study procedures, removal of randomization, and modified visit schedule, and to facilitate participant understanding of the study. NEW INFORMATION is edited to say IPM 027 results will be provided when available, and RISK AND/OR DISCOMFORTS has been updated.
14. Other minor updates, corrections, and clarifications are incorporated

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Rationale

MTN-025/IPM 030 will characterize the safety profile associated with the open label use of the dapivirine vaginal matrix ring (25 mg) as well as characterize adherence to the dapivirine vaginal matrix ring in women who replace the dapivirine vaginal ring monthly. After attending monthly clinic visits until Month 3 of follow-up omen will maintain a quarterly visit schedule. The primary purpose of this Full Version Modification is to streamline the study design by removing the randomization of participants to a monthly vs. quarterly follow-up.

Implementation

This amendment is now official MTN-025 protocol documentation. Prior to implementing the revisions listed below, MTN-025 study sites will submit this Summary of Changes and protocol Version 1.1 to all relevant regulatory entities and IRBs/ECs. Upon receipt of all regulatory and IRB approvals and completion of protocol registration procedures, the protocol modifications listed below will be implemented. With exceptions to modifications to the Protocol Team Roster and updates to the Background Section 2.4.1 and Appendix I, detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** (for additions). Unless otherwise stated, section numbers reflect the current version of the protocol.

Detailed Listing of Revisions New to Version 2.0

1. Protocol Team Roster, the following individual was removed: Jackson, Arbee.

2. Protocol Team Roster, the following individuals were added:

Zakir Gaffoor, M Med Sci
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3. Protocol Team Roster, Malawi CRS was renamed Lilongwe CRS:

~~Malawi~~**Lilongwe CRS**

4. In Section 1, PROTOCOL SUMMARY, edits are made: to clarify that the Decliner Population: Former MTN-020 participants who decline participation in the main MTN-025 study must meet eligibility criteria:

Decliner ~~Group~~**Population**: Former MTN-020 participants who decline participation in the main MTN-025 study **and meet eligibility criteria as described in Sections 5.4 and 5.5**

Section 1, PROTOCOL SUMMARY, Study Design: Randomization information was removed:
Phase 3B, open-label, multi-site~~, randomized~~ trial
Following demonstration of safety and efficacy of the dapivirine vaginal ring in MTN-020, eligible MTN-020 participants will be offered enrollment into MTN-025, a trial designed to obtain additional safety and adherence data in women ~~randomized to monthly vs. quarterly follow-up.~~**.**

5. Section 1, PROTOCOL SUMMARY, Study Design: Text added about the potential extension of follow-up:

Follow-up may be extended beyond 13 months based on need and requirements and with the necessary approvals.

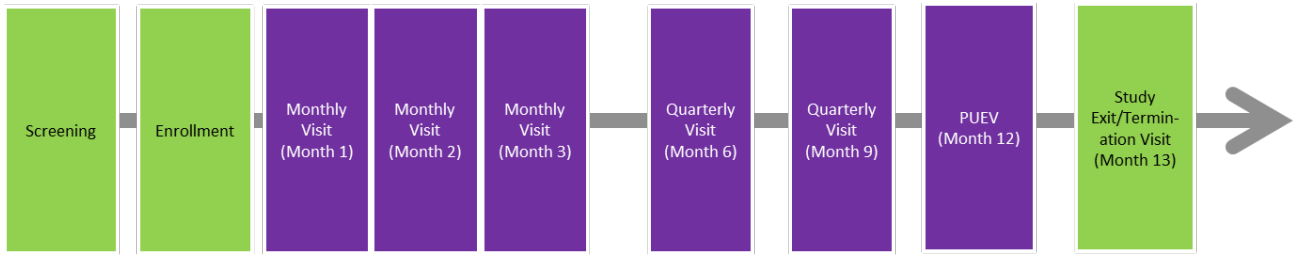
6. Section 1, PROTOCOL SUMMARY, Study Regimen, randomization information was removed:

~~MTN-025 participants are to be randomized to one of two types of follow-up:~~
~~Monthly~~
~~Quarterly~~

7. Section 1, PROTOCOL SUMMARY, Study Regimen, text added about extension of follow-up:

The study follow-up schedule will be monthly for the first three months, then quarterly thereafter (Figure 1), reflecting a transition to a more real-world type of follow-up (versus a clinical trial approach) that would be important for informing implementation.

8. Section 1, PROTOCOL SUMMARY, Figure 1: Study Schedule has been updated as follows:



9. In Section 1, Primary Objectives, 1 and 2 were updated to reflect the lack of randomization:

1. To characterize the safety profile associated with the open label use of the dapivirine vaginal matrix ring (25 mg) in women~~, and to assess safety when randomized to a monthly vs. quarterly follow-up schedule~~

2. To characterize adherence **to** the open label use of the dapivirine vaginal matrix ring (25 mg) in women ~~and to compare adherence when randomized to a monthly vs. quarterly follow-up schedule~~

10. In Section 1, Exploratory Objectives, follow-up schedule is adjusted:

To assess the feasibility of a ~~one-month vs. three-month~~**quarterly** follow-up **visit** schedule

11. In Section 1, Exploratory Endpoints, edits are made for clarity and in fidelity with changes mentioned elsewhere:

- Feasibility~~ of one month vs. three month follow-up~~**:**
- Visit retention ~~by arms~~
- Proportion of returned rings (used and unused) ~~by arms~~

12. In Section 2.1, Microbicides and Human Immunodeficiency Virus (HIV) Prevention, reference to MTN-020 data was removed:

~~The MTN-025 protocol will be updated with MTN-020 safety and efficacy data, once available.~~

13. In Section 2.1, Microbicides and Human Immunodeficiency Virus (HIV) Prevention, edits are made for clarity:

For a microbicide to be ~~most~~ effective, it is essential that it is used correctly and consistently, and **importantly,** is acceptable to the user.

14. In Section 2.3.2, Condom Compatibility Studies of Dapivirine, information regarding the condom functionality studies was added.

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.

15. Section 2.4.1, Clinical Studies of Dapivirine Vaginal Rings, data has been updated throughout to reflect the new Investigator's Brochure

16. In Section 2.4.1, Clinical Studies of Dapivirine Vaginal Rings, reference to other ongoing MTN trials was removed:

Efficacy and safety results from MTN-020 and IPM 027 ~~and other ongoing (as of Q1 2014) clinical trials, including the adolescent trial (MTN-023/IPM 030) and the post-menopausal trial (MTN-024/IPM 031)~~ will be made available to MTN-025 participants.

17. In Section 2.7.1, Study Design, edits are made and comments are added.

MTN-025 will contribute to this evidence base by describing the safety outcomes with a quarterly monitoring schedule for women using an ARV-based HIV prevention intervention. Safety data will be forwarded to regulatory entities

The primary focus of MTN-025 is the collection of additional adherence and safety data~~,~~ ~~including the examination of multiple approaches to follow-up and safety monitoring (monthly vs. quarterly). Further~~ **further**, MTN-025 will examine incidence of HIV-1 infection and explore the way in which ~~people~~**participants** adopt this biomedical prevention method and incorporate it into the context of their everyday lives.

MTN-025 will contribute to this evidence base by describing the safety outcomes ~~associated~~ with ~~both monthly and~~**a** quarterly monitoring schedule~~s~~ for women using an ARV ~~for~~**-based** HIV prevention **intervention**.

18. In Section 3.1, Primary Objectives, updates to ensure consistency with Section 1.0:

1.) To characterize the safety profile associated with the open label use of the dapivirine vaginal matrix ring (25 mg) in women~~, and to assess safety when randomized to a monthly vs. quarterly follow-up schedule~~

2.) To characterize adherence **to** the open label use of the dapivirine vaginal matrix ring (25 mg) in women ~~and to compare adherence when randomized to a monthly vs. quarterly follow-up schedule~~

19. In Section 3.3, Exploratory Objectives, edits are made modifying follow-up schedule:

To assess the feasibility of a ~~one-month vs three-month~~**quarterly** follow-up **visit** schedule

20. In Section 4.1, Identification of Study Design, edits are made including:

The study will assess the safety of and participant adherence to a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine.

The MTN-025 trial, HOPE, is a multi-site, open-label, ~~randomized,~~ Phase 3B trial that will be implemented if the dapivirine VR is found to be a safe and an effective HIV prevention method in the MTN-020 trial. Eligible **former** MTN-020 HIV-uninfected participants will ~~be randomized to either a~~**attend** monthly ~~or a~~**study visits until the third month of follow-up and then** quarterly ~~follow-up schedule.~~**visits thereafter.** The study will ~~compare~~**assess** the safety of and **participant** adherence to ~~dapivirine (25 mg) in a~~ silicone elastomer vaginal matrix ring ~~between the two follow-up schedules~~**containing 25 mg of dapivirine**.

21. In Section 4.3, Description of Study Population, the Decliner Population name has been updated:

Decliner ~~Group~~**Population**: Former MTN-020 participants who decline participation in the main MTN-025 study and meet eligibility criteria as described in Sections 5.4 and 5.5

22. Version 1.0, Section 4.5, Study Groups, was removed:

4.5 ~~Study Groups~~
~~Study arms include monthly and quarterly follow-up arms as defined in Table 4~~
Table 4: ~~Study Regimen~~

~~Group~~	~~Group Description~~	~~Follow-Up~~
~~A~~	~~Dapivirine VR, containing 25 mg dapivirine~~	~~Monthly~~
~~B~~	~~Dapivirine VR, containing 25 mg dapivirine~~	~~Quarterly~~

23. In Section 4.6, Expected Duration of Participation, edits are made::

The majority of former ASPIRE participants will complete approximately 13 months of follow-up, see Section 10.4 for additional details. **Follow-up may be extended beyond 13 months based on need and requirements and with the necessary approvals.**
Visits may be completed within specified windows around target dates. ~~-~~Detailed information regarding visit windows will be described in the MTN-025 **Study Specific Procedures (**SSP**)** Manual.

24. In Section 5.1, Selection of the Study Population, one edit is made:

    Decliner ~~Group~~**Population**: Former MTN-020 participants who decline participation in the main MTN-025 study, and who meet inclusion and exclusion criteria in Sections 5.4 and 5.5, will be invited to complete behavioral assessment(s).

25. In Section 5.1.2, Retention, edit is made removing randomization language:

    Once a participant is enrolled~~/randomized~~ into the HOPE trial, the study site will make every effort to retain the participants in follow-up to minimize possible bias associated with loss-to-follow-up.

26. In Section 5.3, Exclusion Criteria, edit is made removing randomization language:

    Note: PEP use at Screening is not exclusionary. Participants may be enrolled~~/randomized~~ after the PEP regimen is complete and a negative HIV test is documented within 56 days of providing informed consent for Screening.

27. In Section 5.3, Exclusion Criteria, edit is made allowing for possibility of MTN-025 full participation for decliners:

    Note: Participation in the 'Decliner Population' does not preclude MTN-025 full study participation.

28. In Section 5.3, Exclusion Criteria, an edit is made removing randomization language:

    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.

29. In Section 5.4, Inclusion Criteria, MTN-025 Decliner Population Only, edits are made:

    MTN-025 Decliner ~~Group~~**Population** participants must meet all of the following criteria to be eligible for inclusion in the study:

    4) Able and willing to perform the Decliner ~~Group~~**Population** study procedures

30. In Section 5.5, Exclusion Criteria, MTN-025 Decliner Population Only, edits are made:

    MTN-025 Decliner ~~Group~~**Population** participants who meet the following criteria will be excluded from the study:

31. In Section 6.1, Regimen, comments are added

    All participants will receive a vaginal ring containing 25 mg of dapivirine to be worn monthly. One new ring will be inserted each month. Participants will ~~be randomized to either~~**attend** monthly ~~or~~**clinic visits until month three and then will present to the clinic at** quarterly ~~follow-up~~**visits thereafter. Participants are able to visit the clinic for any reason in between the scheduled** visits.

32. In Section 6.3.1, Dapivirine VR, comments are added:

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

33. In Section 6.4.2, Study Product Dispensing, second, third and fourth paragraphs were edited:

~~Participants randomized to~~**During each of the** monthly ~~follow-up~~**clinic** visits **participants** will receive a new ring ~~at each visit~~. If the participant is unable to attend her next scheduled visit it is up to the discretion of the IoR to provide an additional ring(s). All such circumstances must be documented fully by the IoR/designee as described in the MTN-025 SSP Manual.

~~Participants randomized to~~ **When participants enter the** quarterly follow-up ~~visits~~**phase, they** will be dispensed three rings at each study visit or **be given** the option of returning to the site pharmacy or the clinic (based on site dispensing capacity) **each month** to obtain a new vaginal ring each month~~.~~ **(e.g., if they do not feel comfortable having a supply of two additional unused rings at home).** Participant's preference regarding product dispensation and their choice will be documented.

The pharmacist will only dispense one ring per month or up to three rings per quarter depending on the participant's regimen. If a participant requires an additional ring for any reason, at a time other than when she is scheduled to receive one, ~~she will~~**additional product may** be ~~required to attend~~**dispensed at** the ~~clinic for an interim visit~~**discretion of the IoR**.

34. In Section 6.7, Condoms, edits are made to the first and last sentences:

All participants will be offered ~~male~~ condoms.[…] Study staff may also offer guidance on the use of the female condoms upon participant request, see **MTN-025** SSP for additional details.

35. In Section 7, Study Procedures, edits are made and comment is added to the last sentence:

Detailed instructions to guide and standardize procedures across sites ~~(~~**,** including the conduct of off-site study visits~~)~~ **and the follow-up schedule for participants who enroll after the prime accrual period** are provided in the MTN-025 ~~Study Specific Procedures (~~SSP~~)~~ Manual available at http://www.mtnstopshiv.org/studies.

36. In Section 7.3, Table 7, Enrollment Visit, one procedure has been removed:

~~Randomization~~

37. In Section 7.4.1, Table 8, Follow-up Visits: Months 1 and 2 headings have been updated as follows:

Months 1~~,~~ and 2~~, 4, 5, 7, 8, 10, 11~~

38. In Section 7.4.2, Quarterly Visits, edits are made:

Procedures listed below will occur at quarterly visits (i.e., Months 3, 6, 9 ~~Participants in both study arms will undergo~~**), until** the ~~following procedures quarterly~~**Product Use End Visit**.

39. In Section 7.4.2, Quarterly Visits, Table 9 has been updated with 'Quarterly Visits'.

40. In Section 7.4.2, Quarterly Visits, Table 9 has been updated to require that the following procedures only be performed if indicated: Physical examination, NAAT for GC/CT, and rapid test for Trichomonas

41. In Section 7.4.3 Product Use End Visit (PUEV) edits are made:

    Participants ~~in both study arms~~ will undergo the following procedures at ~~Month 12~~**the Product Use End Visit**.

42. Throughout Section 7.0 the collection of plasma has now been specified to be collected for dapivirine drug level testing and for archive.

43. In Section 7.5, MTN-025 Decliner Population, Screening and Enrollment Procedures edits are made to maintain consistency with the rest of the protocol.

44. In Section 7.6.1, Participants Who Become Infected with HIV, the SSP has been specified:

    Please reference the **MTN-025** SSP for additional details (http://www.mtnstopshiv.org/studies).

45. In Section 7.6.2, Participants Who Become Pregnant, the SSP has been specified:

    See **MTN-025** SSP Manual for additional guidance.

46. In Section 7.8, MTN-025 Decliner Population, edits are made:

    MTN-025 Decliner ~~Group~~Population
    Former ASPIRE participants who decline or express no interest in joining the MTN-025 trial either prior to screening or prior to enrollment, will be invited to complete behavioral assessment(s), which may include IDI(s) to explore reasons for disinterest**, individuals who are found eligible and who take part are referred to as the MTN-025 Decliner Population**.

47. In Section 7.12, HIV Infection (Secondary Endpoint) Determination, edits are made:

    First paragraph-

    Prior to study initiation, all sites will have validated this algorithm in accordance with the policies described in the MTN Manual of ~~Operations~~**Operational Procedures** (MOP) (http://www.mtnstopshiv.org/node/187). All sites will participate in ongoing proficiency testing of their HIV testing procedures throughout the course of the study. The HIV test kits used at each site are pre-approved by the MTN ~~Laboratory Center (LC);~~**LC;** at each testing time point when rapid tests are used at least one FDA-approved rapid test kit is used.

    Fourth paragraph, second through the fifth sentence-

Further, as part of quality control, researchers may need to look at short pieces of non-coding repetitive DNA sequence (3-7 base pairs) from blood ~~in the event of~~**if there is a question regarding** sample ~~mix up~~**integrity**. This test will only let researchers know the number of times this short segment is repeated and not specific genes or specific sequences of base pairs. This sequence element does not contain any information about genes~~,~~**.** ~~t~~**T**herefore researchers will not be able to identify if participants are predisposed to specific diseases or any other genetic information based on this information.

48. In Section 8.1, Safety Monitoring, edits are made:

A sub-group of the Protocol Team, including the Protocol Co-Chairs, DAIDS Medical Officer, Protocol Safety Physician(s), **IPM Representative,** and SDMC Clinical Affairs Safety Associate will serve as the Protocol Safety Review Team (PSRT).

49. In Section 8.3.1, Adverse Events, first paragraph comments are added:

This definition is applied to all study ~~groups, and is applied to both groups beginning~~**participants** at the time of enrollment ~~(i.e.,~~**. Enrollment is defined as** once a participant **has provided written informed consent for enrollment and it has been determined she** is ~~randomized~~**eligible for the study (based on IoR or designee sign-off after all protocol-specified inclusion/exclusion criteria have been assessed**).

50. In Section 8.4.1, Adverse Event Reporting to DAIDS, edits are made:

For each study participant, expedited AE reporting will be undertaken throughout the scheduled duration of follow-up, i.e., from the time of ~~random assignment~~**Enrollment** through study termination.

51. In Section 8.4.4, Expedited AE Reporting Period, comments are added:

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

52. In Section 10.1, Overview and Summary of Design, edits are made:

This is a Phase 3B, open-label, multi-site~~, randomized~~ trial. A sample size of approximately 1000-2500 participants will be ~~randomly assigned in a 1:1 ratio to either monthly or quarterly follow-up~~**followed for approximately 13 months, with approximately 12 months of study product use**. The two main goals of the trial are:

1. To characterize the safety profile associated with the open label use of the dapivirine vaginal matrix ring (25 mg) in women~~, and to assess safety when randomized to a monthly vs. quarterly follow-up schedule~~

2. To characterize adherence **to** the open label use of the dapivirine vaginal matrix ring (25 mg) in women ~~and to compare adherence when randomized to a monthly vs. quarterly follow-up schedule~~

53. In Section 10.3, Sample Size, comments are added

The final number is dependent upon ~~both the final number enrolled in MTN-020, ASPIRE, and~~ the proportion of ASPIRE participants who **are eligible and** choose to enroll into MTN-025, HOPE.

54. In Section 10.4, Participant Accrual, Follow-up and Retention comment is added

~~Because of the potential to randomize to a monthly or a quarterly follow-up schedule, it~~**It** is anticipated that the study will close to accrual 4 months ahead of the anticipated closure of the study. Based upon the timing of ~~when a~~ participant ~~is enrolled~~**enrollment**, follow-up may last approximately 4-13 months. **Follow-up may be extended beyond 13 months based on need and requirements and with the necessary approvals.**

55. Section 10.5 Randomization has been deleted:

~~At the enrollment visit, participants will be randomly assigned to one of the two follow-up arms (monthly vs. quarterly) in a 1:1 ratio. The randomization scheme will be stratified by site and will be generated and maintained by the MTN SDMC. The randomized assignments will be in blocks to keep the balance of equal allocation. The SDMC will provide each study site with a series of numbered, sealed envelopes containing the randomization assignment for each participant. The envelopes will be assigned sequentially by site staff. The MTN SDMC will coordinate the randomization procedures, which will be specified in the SSP Manual. Assignment of the clinic randomization envelope is considered the effective act of participant randomization.~~

56. In Section 10.8.1 Primary Safety Analysis text is removed:

Consistent with the primary safety objective, this analysis will characterize the safety profile for the overall population ~~and the two arms. Because women in the monthly arm will be seen more frequently, we expect that more safety events will be recorded that would otherwise go unreported or unobserved with less frequent follow-up. Therefore, under this design a comparison between the arms is most appropriate for AEs that would be captured regardless of frequency of follow-up. These include the two key secondary outcomes of drug resistance and breakthrough infections. Those analyses will be covered in Section 10.9. As a supporting analysis, rates of AEs between the arms at quarterly visits will be compared, recognizing that this may be imperfect as well since monthly participants may have AEs resolved before a quarterly visit that may have remained unresolved were they on the quarterly schedule. Therefore, the AE rate in the monthly arm may look lower at quarterly visits because the AEs have been resolved.~~**.**

57. In Section 10.7.2 Primary Adherence Analysis comment is made and Figure 2 was deleted

For the primary study aim related to adherence, participants will be categorized as adherent if drug is detected in all quarterly plasma samples when participants are not on a product hold~~.~~ ~~The arms will be compared using a chi-square test for 2x2 tables.~~ **and the proportion of adherent participants with a 95% confidence interval will be reported.**

~~Based on this primary analysis plan, we calculated power under a variety of assumptions. The figure below shows hypothetical adherence rates for the two arms on the x- and y-axes. The curves connect the comparisons for which the comparison has 90% power. Each curve~~

~~represents a hypothetical sample size across both arms ranging from 2500 (representing a potential full study analysis) to 100 (representing a potential within site or subgroup analysis). For example, with a sample size of 1500, if the higher adhering arm has 80% adherence, the study has 90% power to detect a difference between the two arms if the lower adherence arm has adherence of 73% or less. If the sample, size were instead 200, we could detect a difference between an 80% adherent arm and a 59% adherent arm.~~
~~Figure 2: Comparison of Rates of Adherence (Low Group Vs. High Group)~~
~~The analysis described above compares rates of perfect adherence as measured in plasma.~~

58. In Section 10.9 Analysis of Secondary Endpoints edits are made::

59. We will calculate the incidence overall ~~and by arm~~ for each endpoint. Use of new and additional HIV-1 prevention technologies, such as oral PrEP and/or topical vaginal gels, will be captured on standardized data forms and will be taken into account in the analysis of HIV-1 incidence. We will calculate confidence intervals for ~~the differences between arms in~~ incidence rates using the Poisson distribution. ~~We anticipate this analysis to have low power since we will be comparing two arms in which participants are prescribed an active product that has been proven effective.~~

60. In Section 13.4.1, Risks, edits are made based upon the Treatment-Emergent Adverse Events with Causal Relationship to Dapivirine Ring-004 as Assessed by the Investigator within the Investigator's Brochure:
    - Metrorrhagia
    - **Vaginal** or genital **discharge**
    - Vaginal candidiasis
    - ~~Vaginal bleeding~~
    - ~~Headache~~
    - ~~Fatigue~~
    - ~~Vulvovaginal or genital itching~~
    - ~~Abdominal discomfort~~
    - ~~Abdominal pain~~
    - Urinary ~~**incontinence**~~**tract infection**
    - ~~Nausea~~
    - ~~Vaginal or genital discharge~~

61. In Section 13.5, Informed Consent Process, edits are made::

Written informed consent will also be obtained for long-term specimen storage and possible future testing, for off-site clinic visits as needed, as well as for participation in the 'Decliner Cohort' **Population'**. […] Further, participation in the 'Decliner ~~Cohort~~'**Population'** does not preclude MTN-025 full study participation **in the future**.

First Bullet removed-

- ~~Randomization and the importance of participants in both study groups to the success of the study~~

62. Appendix I: Schedule of Study Visits and Evaluations has been edited to maintain consistency with Section 7.0, Study procedures.

63. Appendix IV: Sample Informed Consent Document (Screening) edits are made:

PURPOSE OF THE SCREENING TESTS AND THE STUDY-
The main purpose of these screening exams and tests is to find out if you can join this research study. This research study will test if a vaginal ring containing the medicine dapivirine is used as directed and found to be safe in participants who attend clinic visits ~~at different time points (monthly vs. every three months).~~**.** Women will be in this study for approximately 13 months depending upon when they enroll in the study; however this period could be shorter or longer than anticipated. **You will be notified if the study extends beyond 13 months.**

~~**STUDY GROUPS**~~
~~If you join MTN-025, you will be in one of two study groups. Both groups will use the same ring containing dapivirine, but the timing of clinic visits will differ. Half of the women will be in a study group that will be asked to come to the clinic for monthly visits. The other half of the women will come to the clinic for visits every three months. You will be assigned to a group by random chance, like flipping a coin. Neither you nor the staff can decide which follow-up schedule you will be assigned. Both of the study groups are important to this study.~~

64. Appendix V: Sample Informed Consent (Enrollment) edits are made:

PURPOSE OF THE STUDY-

This research study will test if a vaginal ring containing the medicine dapivirine is used as directed and found to be safe in participants who attend clinic visits ~~at different time points (monthly vs. every three months).~~**.** Women will be in this study for approximately 13 months depending upon when they enroll in the study; however the duration of study participation could be shorter or longer than anticipated. **You will be notified if the study extends beyond 13 months.**

STUDY GROUPS-

~~**STUDY GROUPS**~~
~~If you join MTN-025, you will be randomly assigned (like flipping a coin) to one of two study groups. Both groups will use the same ring containing dapivirine, but the timing of clinic visits will differ. Half of the women will be in a study group that will be asked to come to the clinic for monthly visits. The other half of the women will come to the clinic for visits every three months. You will be assigned to a group by random chance, like flipping a coin. Neither you nor the staff can decide which follow-up schedule you will be assigned. Both of the study groups are important to this study.~~

WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN THE MTN-025 STUDY-

If you decide to enroll in the study, you will have a clinic visit today and monthly ~~or every~~**for the next** three months ~~thereafter, depending upon which group you are randomly assigned to.~~ **, then quarterly thereafter.**

Risks of Study Drugs

- Vaginal bleeding
- ~~Headache~~
- ~~Fatigue~~
- ~~Itching on the external parts of~~ **at irregular intervals, particularly between your ~~genitals~~ expected menstrual periods**
- ~~Abdominal discomfort~~
- ~~Abdominal pain~~
- ~~The loss of bladder control~~
- ~~Nausea~~
- Vaginal or genital discharge
- **Yeast infection**
- Urinary tract infection

NEW INFORMATION-

In addition to being tested as part of the ASPIRE trial, the ring was also tested in IPM 027 ~~[INSERT IPM 027 DESCRIPTION AND RESULTS AND/OR UPDATE, IF AVAILABLE, HERE].~~ **. IPM 027 results will be provided to participants when they become available.**

65. Appendix VI: Sample Informed Consent Document (MTN-025 Decliner Population) to highlight that the 'Decliner Group' will now be referred to as the 'Decliner Population' and redundant text in the RISK AND/OR DISCOMFORTS section has been removed:

~~[Sites to modify based upon their institutional policy: In the unlikely event that you get injured as a result of your study participation, it is important that you know the US National Institutes of Health (NIH) does not have a mechanism to provide direct compensation for research-related injury.]~~

LETTER OF AMENDMENT #01 TO:

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

Version 2.0, dated 16 December 2014

DAIDS Protocol #11985
IND #108,743

Date of Letter of Amendment: 11 April 2016

Site Instruction

The following information impacts the MTN-025 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation. The following information impacts the sample informed consent. Your IRB/EC will be responsible for determining the process of informing participants of the contents of this Letter of Amendment (LoA).

Implementation

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. DAIDS sites are still required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). DAIDS sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

Summary of Revisions

This LoA does not impact the overall design or the study visit schedule for MTN-025.

The primary purpose of this LoA is to incorporate the primary results from IPM 027 (The Ring Study) and MTN-020 (ASPIRE), two trials that evaluated the safety and efficacy of the dapivirine vaginal ring (Ring-004). This LoA also adds two new exploratory objectives for characterizing ASPIRE participants who do not accept study product in MTN-025 and to explore alternative markers of product adherence, including participant self-report and analysis of hair samples. This LoA removes the protocol requirement to use FDA-approved HIV testing kit for HIV infection confirmation, allows for post-infection/pre-seroconversion testing of plasma samples, modifies the list of procedures that should stop after an HIV seroconversion, allows the use of audio files as source documents for in-depth interview data, explicitly allows for the concomitant use of oral tenofovir-based PrEP, updates the DAIDS Adverse Event (AE) Grading Table from Version 1.0 to 2.0, updates the risks associated with the dapivirine vaginal ring, updates DAERS contact information, updates the Protocol Team Roster, and makes other minor revisions to the protocol.

Unless otherwise noted, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions

The following revisions (#1-13) incorporate primary results from IPM 027 (The Ring Study) and MTN-020 (ASPIRE), including edits related to the start of MTN-025 implementation being contingent upon those two studies' findings.

1. In Section 2.1, Microbicides and Human Immunodeficiency (HIV) Prevention, after the second sentence in the fifth paragraph:

   The results from two recently completed Phase 3 safety and efficacy trials of the dapivirine VR, MTN-020 (ASPIRE) and IPM 027 (the Ring Study), both of which found the VRs to be safe and effective in reducing HIV-1 infection in healthy female adults in sub-Saharan Africa when used for one month and replaced monthly, would indicate the advisability of initiating ~~Initiation of~~ the MTN-025 study of the dapivirine VR **as an open-label extension of MTN-020 (ASPIRE).** ~~will be contingent upon demonstration of the safety and efficacy of the product in the ongoing MTN-020 (ASPIRE) study. The specific level of effectiveness required to trigger activation of the MTN-~~

~~025 study will be decided upon following discussions with key stakeholders including regulatory authorities, community representatives, and sponsoring agencies.~~

2. A new, ***Extended Safety and Efficacy***, sub-section was created in Section 2.4.1, *Clinical Studies of Dapivirine Vaginal Rings*, above the twelfth paragraph in the Safety subsection that starts "In March of 2012, IPM 027,":

Extended Safety and Efficacy

In March of 2012, IPM 027, also known as The Ring Study, was initiated. IPM 027 ~~is~~**was** a randomized, double-blind, placebo-controlled efficacy and long-term safety study that ~~will enroll 1,650~~ **enrolled 1959** healthy, HIV-uninfected women, ages 18-45. **Approximately 1762 women in South Africa and 197 in Uganda were randomized in a 2:1 ratio to receive either a dapivirine ring or a placebo ring.** ~~The study is being conducted in South Africa and Uganda.~~ Study participants ~~will use~~**used** either the dapivirine ring or the placebo ring every four weeks over approximately two years. The main goals of The Ring Study ~~are~~**were** 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**d** measuring the incidence of curable STIs, HIV-2 and pregnancy; monitoring ring acceptability (how well women like**d** using the ring) and adherence (if women use**d** the ring as intended) as reported by the study participants; and tracking the development of any HIV-1 drug resistance in participants who ~~become~~**became** HIV positive during the study. ~~The study is anticipated to conclude in 2015/2016.~~

The median age at enrollment was 25 years, and 91% were unmarried. At the data cut-off point, the total number of person years of follow-up was 2805, and 761 women had completed the two year follow-up period. A total of 133 post-randomization HIV-1 infections occurred: 77 among women assigned to dapivirine ring (incidence 4.08 per 100 person-years) and 56 among women assigned to placebo (incidence 6.10 per 100 person-years). Dapivirine vaginal ring reduced the risk of HIV-1 infection by 30.7% (95% CI: 0.90-51.5%; p=0.0401) relative to placebo. A 37.5% (95% CI: 3.5-59.5%) reduction in HIV-1 infection was observed in a subgroup analysis of women older than 21 years. Product-related AEs included metrorrhagia, menometrorrhagia, pelvic discomfort/pain, suprapubic pain and application site pain. There were no statistically significant differences in the frequency of the primary safety endpoints between the study arms. Further, there was no overall difference between NNRTI resistance profiles.

MTN-020, A Study to Prevent Infection with a Ring for Extended Use (ASPIRE), ~~is~~ **was** 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~~ **was** conducted in HIV-uninfected women, between the age~~s~~ **of** 18 **and-** 45. A total of 2629 women from Malawi, South Africa, Uganda, and Zimbabwe ~~have~~ enrolled in the trial. Participants replace**d** the ring monthly for a minimum of one year. MTN-020 ~~aims~~ **aimed** to determine the safety and efficacy of the dapivirine ring in preventing HIV-1 infection among healthy, sexually active, HIV-uninfected women when inserted vaginally once every 4 weeks. Additional goals of MTN-020 include**d** the assessment of participant acceptability and adherence to the investigational product, HIV-1 drug resistance mutations among participants who acquire**d** HIV-1 infection**,** and establishing steady state drug concentrations in the study population. ~~The study is anticipated to conclude in 2015.~~ **Results were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) February 2016 (Abstract #109LB) and published in the New England Journal of Medicine (N Engl J Med. Epub 22 Feb 2016. DOI: 10.1056/NEJMoa1506110).**

A total of 168 HIV-1 infections occurred: 71 among those assigned the dapivirine vaginal ring and 97 among those assigned the placebo ring (incidence 3.3 and 4.5 per 100 person-years, respectively). Dapivirine ring resulted in a 27% (95% CI: 1-46%, p=0.046) relative reduction in HIV-1 incidence overall and a 37% (95% CI: 12-56%, p=0.007) reduction in an analysis defined early in the study excluding data from two study sites with lower retention and adherence. In pre-defined as-randomized subgroup analyses, HIV protection differed significantly by age, with a 61% reduced risk of HIV for women ≥ 25 years [CI: 32%, 77%)] p<0.001, and 10% reduced risk for women < 25 years (CI: -41%, 43%) p=0.64. A post-hoc analysis was conducted to further explore this result, which indicated that a 56% (95% CI: 31-71%, p<0.001) reduction among women older than 21 years of age, and no HIV-1 protection for women aged 18-21, with objective markers of adherence lower in this subgroup compared to women older than 21. The rate of adverse events was similar between study arms as was the frequency of antiretroviral resistance in those who acquired HIV-1.

There were no statistically significant differences in the frequency of the primary safety endpoints between the study arms or in other adverse events commonly detected in the study population. Incident sexually transmitted infections occurred at a similar rate in the two study arms. Finally, among those acquiring HIV-1, detection of non-nucleoside reverse transcriptase inhibitor mutations did not differ by study arm (8/68 assigned dapivirine and 10/96 assigned placebo, p=0.80).

The dapivirine ring was safe and effective in preventing HIV infection in both ASPIRE and The Ring Study. Results suggest the dapivirine ring could be an important HIV prevention option for women at risk of HIV infection.

3. The following revisions have been made to Section 2.7.1, Study Design, after the first sentence in the first paragraph:

   ~~Upon demonstration of the safety and effectiveness of~~ **Given that** the dapivirine VR **was found to be safe and effective** in the MTN-020 **study**, implementation of the follow-on trial, MTN-025, will commence

4. The following revisions have been made to Protocol Summary, Study Design:

   ~~Following demonstration of safety and efficacy of~~ **Given that** the dapivirine vaginal ring **was found to be safe and effective** in **the** MTN-020, eligible MTN-020 participants will be offered enrollment into MTN-025, a trial designed to obtain additional safety and adherence data in women.

5. The following revision has been made to Section 2.7.1, Study Design, fourth paragraph:

   […] (Ring-004) when inserted monthly in healthy, HIV-uninfected, not pregnant, sexually active research-experienced women~~ should efficacy be demonstrated in MTN-020~~.

6. The following revisions have been made to Section 4.1, Identification of Study Design, first sentence:

   The MTN-025 trial, HOPE, is a multi-site, open-label, Phase 3B trial~~ that will be implemented if the dapivirine VR is found to be a safe and an effective HIV prevention method in the MTN-020 trial~~.

7. The following revisions have been made to Section 5.1, Selection of the Study Population, first sentence:

   ~~If safety and efficacy of the dapivirine vaginal ring are demonstrated in MTN-020 (ASPIRE);~~ MTN-025 (HOPE)~~, will be~~ **is being** implemented as a follow-on trial **to MTN-020 (ASPIRE), which demonstrated safety and efficacy of the dapivirine VR**.

8. The following revisions have been made to Section 13.4.2, Benefits, first sentence of first paragraph:

   ~~MTN-025 (HOPE) will only be implemented if~~**Given that** the dapivirine vaginal ring as tested in MTN-020 (ASPIRE) **was**~~is~~ found to be safe and effective, ~~therefore,~~ participants in the HOPE study will experience the direct benefit of using a product that has been found to be safe and effective in preventing HIV acquisition and will be considered for potential regulatory approval.

9. The following revisions have been made to Appendix IV, Sample Informed Consent Document (Screening), Informed Consent sub-section, after the second sentence of the first paragraph:

   ~~The research study you participated in,~~ MTN-020~~:~~ **(**ASPIRE**)**, *A Study to Prevent Infection with a Ring for Extended Use*, showed that the dapivirine vaginal ring ~~can reduce the chances of HIV-uninfected women from getting the HIV virus by [SITES TO INSERT: from X to X percent]~~**prevented approximately one third of HIV infections. Among women older than 21, who used the ring more consistently than younger women, more than half of HIV infections were prevented**. The study also learned that the dapivirine vaginal ring is ~~[SITES TO INSERT:~~ safe (meaning that **VR use** ~~they do not produce significant~~ **did not cause** health problems~~ in persons who take them~~)~~]~~ ~~when used by HIV-uninfected women~~. **In addition to being tested as part of the ASPIRE trial, the ring was also tested in IPM 027. IPM 027 results were similar to those in ASPIRE, demonstrating the dapivirine ring is safe, well-tolerated and effective, reducing HIV-uninfected women's chances of getting the HIV virus by approximately one third.** Only through the participation of volunteers in clinical research can the safety and effectiveness of medicine be better understood. ~~More data is needed on the safety of the dapivirine vaginal ring. Because you took part in the ASPIRE study, y~~**Y**ou are being offered the opportunity to use the safe and effective dapivirine vaginal ring as part of this new study.

10. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), Informed Consent sub-section, after the first sentence of the first paragraph:

    ~~The research study you participated in,~~ MTN-020~~:~~ **(**ASPIRE**)**, *A Study to Prevent Infection with a Ring for Extended Use*, showed that the dapivirine vaginal ring ~~can reduce HIV-uninfected women's chances of getting the HIV virus by~~

~~[SITES TO INSERT: from X to X percent]~~**prevented approximately one third of HIV infections. Among women older than 21, who used the ring more consistently than younger women, more than half of HIV infections were prevented**. The study also learned that the dapivirine vaginal ring is ~~[SITES TO INSERT:~~ safe (meaning that **VR use** ~~it~~ does not cause ~~significant~~ health problems)~~] when used by HIV-uninfected women~~. ~~More data is needed on the safety of the dapivirine vaginal ring. Because you took part in the ASPIRE study, y~~ **In addition to being tested as part of the ASPIRE trial, the ring was also tested in IPM 027. IPM 027 results were similar to those in ASPIRE, demonstrating the dapivirine ring is safe, well-tolerated and effective, reducing HIV-uninfected women's chances of getting the HIV virus by approximately one third. Y**ou are being offered the opportunity to use the safe and effective dapivirine vaginal ring as part of this new study.

11. The following revision has been made to Appendix V, Sample Informed Consent Document (Enrollment), What do I have to do if I decide to take part in the MTN-025 study? sub-section titled "If you become infected with HIV", first sentence of second paragraph:

    It may be necessary, depending upon local and national health requirements, for study staff to report diseases, including HIV, identified among MTN-02~~0 (ASPIRE)~~**5 (HOPE)** study participants.

12. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), New Information sub-section, third and fourth sentence of the first paragraph, and second sentence of the second paragraph:

    ~~[SITES TO INSERT MTN-020 DATA HERE]. In addition to being tested as part of the ASPIRE trial, the ring was also tested in IPM 027. IPM 027 results will be provided to participants when they become available.~~

    The HIV prevention researchers working on ~~this~~ MTN-025 (HOPE) are committed to sharing any data with you that becomes available, regardless of the product, if it is found to be effective in preventing the transmission of HIV.

13. The following revisions have been made to Appendix VI, Sample Informed Consent Document (MTN-025 Decliner Population), Purpose of the Decliner Population sub-section, after the first sentence:

    MTN-025~~,~~ is a study that provides ~~former ASPIRE participants with~~ **eligible women** access to the dapivirine vaginal ring~~, a product that has been shown to reduce the chances of women from getting the HIV virus by~~**.** ~~[To be updated: X to X percent]~~. **MTN-020: (ASPIRE), A Study to Prevent Infection with a Ring for Extended Use, showed that the dapivirine vaginal ring prevented approximately one third of HIV infections were prevented. Among women older than 21, who used the ring more consistently than younger women, more than half of HIV infections were prevented.** The study also learned that the dapivirine vaginal ring is ~~[To be updated:~~ safe (meaning that ~~#~~ **VR use** does not ~~produce significant~~ **cause** health problems**).** ~~in persons who take it].~~

The following revisions (#14-37) have been made to add a new exploratory objective: characterization of participants who do not accept study product and to make the necessary changes in the protocol to satisfy the objective/endpoint:

14. The following bullet point items have been added to Protocol Summary, Exploratory Objectives, and to Section 3.3, Exploratory Objectives, to add the one new exploratory objective:

    6. To characterize the MTN-020 participants who do not accept study product in MTN-025

15. The following bullet point items have been added to Protocol Summary, Exploratory Endpoints, to add the one new exploratory objectives' endpoints:

    6. Characterization of MTN-020 participants who do not accept study product in MTN-025
    - **Participant report of the factors that led to her decision to not accept study product**

16. The following revision has been made to Protocol Summary, Study Regimen, to clarify that HOPE participants have a choice regarding whether to accept study product:

    Participants will ~~receive~~**be offered** a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine to be replaced each month for ~~a total period of~~**approximately** 12 months of use.

17. The following revision has been made to Section 6.1, Regimen, first two sentences, to clarify that HOPE participants have a choice regarding whether to accept study product:

All participants will ~~receive~~**be offered** a vaginal ring containing 25 mg of dapivirine to be worn monthly. **Participants will be able to choose whether to insert** ~~O~~**o**ne new ring ~~will be inserted~~ each month.

18. The following revision has been made to Section 6.2, Administration, first sentence, to clarify that HOPE participants have a choice regarding whether to accept study product:

    If they choose, ~~The~~ participant**s** will self-insert the study VR monthly.

19. The following revisions have been made to the second and third paragraph within Section 6.4.2, Study Product Dispensing, to clarify that HOPE participants have a choice regarding whether to accept study product:

    ~~During each of the monthly clinic visits participants will receive a new ring.~~ If the participant is unable to attend her next scheduled visit ~~it is up to the discretion of the IoR to provide~~ **provision of** an additional ring(s) may be **provided at the discretion of the IoR as permitted in the SSP**. All such circumstances must be documented fully by the IoR/designee as described in the MTN-025 SSP Manual.

    When participants enter the quarterly follow-up phase, ~~they~~ **those who choose to use study product** will be dispensed three rings at each study visit or be given the option of returning to ~~the site pharmacy or~~ the clinic ~~(based on site dispensing capacity)~~ each month to obtain a new vaginal ring ~~each month~~ (e.g., if they do not feel comfortable having a supply of two additional unused rings at home). Participant's preference regarding product dispensation and their choice will be documented **and updated as needed**.

20. The following revisions have been made to Section 7.3, Enrollment Visit (Day 0), Table 6, Enrollment Visit (Day 0), rows under "Study Product/Supplies" component to ensure that it is clear that study VR use instructions will only be offered to participants if the product is accepted and to allow ASPIRE participants to choose to use study product in MTN-025:

Study Product/Supplies	• Provision of study VR use instructions***** • ~~Provision of~~**Offer and, if accepted, provide** study VR(s)

21. The following revisions have been made to Section 7.4.1, Months 1 and 2, Table 7, Follow-up Visits, Months 1 and 2, rows under "Study Product/Supplies" component; and Section 7.4.2, Quarterly Visits (Months 3, 6, 9), Table 8, Quarterly Visits, rows under "Study Product/Supplies" component, to allow ASPIRE participants to choose to use study product in MTN-025:

Study Product/Supplies	• Provision of study VR use instructions***** • ~~Provision of~~**Offer and, if accepted, provide** study VR(s)

22. The following revisions have been made to Section 7.4.1, Months 1 and 2, Table 7, Follow-up Visits, Months 1 and 2, only row under "Laboratory-Study Product" and second row under "Study Product/Supplies"; Section 7.4.2, Quarterly Visits (Months 3, 6, 9), Table 8, Quarterly Visits, only row under "Laboratory-Study Product" and second row under "Study Product/Supplies"; and Section 7.4.3, Product Use End Visit (PUEV), Table 9, PUEV, Month 12, only row under "Laboratory-Study Product" and second row under "Study Product", to complete procedures as indicated for those participants who choose to use study product in MTN-025:

Study Product	• Adherence assessment(s): Returned study VR**(s)***
Study Product/Supplies	• Removal and collection of used/unused study VR**(s)***

23. The following revisions have been made to Section 7.6.1, Participants Who Become Infected with HIV, second bullet point after second paragraph, Section 7.6.2, Participants Who Become Pregnant, first bullet point; and Section 7.6.3, Participants Who Temporarily Hold or Permanently Discontinue Study Product Use, first bullet point, to clarify that HOPE participants have a choice regarding whether to accept study product:

    - ~~Provision of~~ **Offer and, if accepted, provide** VR, **product use** instructions, **and product** adherence counseling

24. The following bullet point has been added to Section 7.8, Behavioral Evaluations, after the first paragraph, to include assessment of the newly added exploratory endpoint of "participant report of the factors that led to her decision to not accept study product":

    - **Motivations for using or declining to use study product while participating in this research study**

25. The following revisions have been made to Section 7.9, Adherence Counseling, first sentence, to clarify that HOPE participants have a choice regarding whether to accept study product:

    Study product adherence counseling will be provided as a component of the Protocol Adherence Counseling to all study participants by site staff. **Messages will be tailored based on whether or not the participant chooses to accept study product.**

26. The following revisions have been made to Section 10.1, Overview and Summary of Design, second sentence of first paragraph, to clarify that HOPE participants have a choice regarding whether to accept study product:

    A sample size of approximately 1000-2500 participants will be followed for approximately 13 months, with approximately 12 months of study product use **for participants who choose to use the VR**.

27. The following bullet points have been added to Section 13.5, Informed Consent Process, first bullet point after third paragraph, to accommodate MTN-025 participants who do not accept study product in MTN-025:

    - **The importance of study product adherence to its effectiveness**
    - **That all participants may choose not to use study product at any time and still take part in the study**

28. The following revisions have been made to Appendix I, Schedule of Study Visits and Evaluations, last row in the "Laboratory" section and second to fourth rows under "Study Product/Supplies" section for consistency with changes made in Section 7.0:

	SCR	ENR	M. 1 and 2	Quarterly Visits	PUEV	Study Exit/ Term. Visit (~ 1 Month after the PUEV)
Adherence assessment(s): Returned Study VR**(s)**			~~X~~*	~~X~~*	~~X~~*	
STUDY PRODUCT/ SUPPLIES						
Provision of study VR use instructions		~~X~~*	*	*		
~~Provision of~~**Offer and, if accepted, provide** study VR**(s)**		X	X	X		
Removal and collection of used/unused study VR**(s)**			~~X~~*	~~X~~*	~~X~~*	

29. The following revisions have been made to Appendix IV, Sample Informed Consent Document (Screening), Study Product section, second sentence of first paragraph; and to Appendix V, Sample Informed Consent Document (Enrollment), Study Product section, second sentence of first paragraph, to clarify that ASPIRE participants will be offered the vaginal ring MTN-025:

    ~~Unlike ASPIRE, there is no placebo vaginal ring (a ring without the study medicine) in HOPE, so~~ a**A**ll HOPE participants will ~~receive~~ **be offered the use of** a vaginal ring containing dapivirine.

30. The following revisions have been made to Appendix IV, Sample Informed Consent Document (Screening), Purpose of the Screening Tests and the Study, second sentence and to Appendix V, Sample Informed Consent Document (Enrollment), Purpose of the Study section, first sentence:

    This research study will test if a vaginal ring containing the medicine dapivirine is used as directed **by participants** and ~~found to be~~ **is** safe ~~in participants who attend clinic visits~~**when provided on a three-monthly schedule.**

31. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, second and third sentence of first paragraph, to clarify that HOPE participants have a choice regarding whether to accept study product:

    You will ~~insert~~**be offered** a ~~new~~ vaginal ring **to use, with a new ring to be inserted** monthly for approximately 12 months **of use**. For some participants, this period of time may be less, **for instance, if a participant enrolls in the study late or chooses not to insert the vaginal ring every month she is enrolled.** ~~s~~**S**tudy staff ~~will~~**can** provide you with an estimate of how long you will ~~use the~~ **be offered access to the** ring. **Study procedures will be similar regardless of whether or not you choose to use the ring.**

32. The following revision was made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, fifth sentence edited:

You will have a final study visit to check on your health ~~approximately 4 weeks after the final ring is removed~~.

33. The following revision was made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, You will have the following clinical procedures performed, pelvic exam bullet:

    A pelvic examination~~ when the vaginal ring is removed for the final time~~.

34. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, first sentence preceding second bullet point list, to clarify that HOPE participants have a choice regarding whether to accept study product:

    You will be **offered** ~~asked to use~~ a study vaginal ring **to use**.

35. The following sentence has been added to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, at the end of the fourth bullet point in the second set of bullet points, and at the end of the second and fourth bullet points in the fourth set of bullet points, to inform participants that they may receive drug use results:

    You may receive these test results indicating your study product use if you choose to accept the vaginal ring.

36. The following revision has been made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, first bullet point of third bullet point list, to accommodate MTN-025 participants who do not accept study product in MTN-025:

    - **If you chose to accept a ring for use,** ~~Y~~**y**our experience using the vaginal ring, including whether or not the ring was removed from or fell out of your vagina.

37. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study?, In-depth Interview(s) and Group Discussions sub-section, first sentence in the second and third paragraphs, to reiterate that MTN-025 participants who choose not to use study product may still be selected for in-depth interviews and group discussions:

    If you are asked to participate in a group discussion, you will be asked to discuss your use of the study product, your feelings about the study product and trial participation, your vaginal practices and other questions that can help researchers to better understand participants' experiences while taking part in the study**, whether you used the vaginal ring or not**. These discussions will last about one hour.
    […]
    If you are asked to participate in an interview, you will be asked questions about your use of the ring, your preferences and opinions, your experiences with using the ring during sex, ~~and~~ any problems you may have had using the ring**, and whether you used the vaginal ring or not**.

The following revisions (#38-43) have been made to add the new exploratory objective: To explore alternative markers of adherence and to make the necessary changes in the protocol to satisfy the objective/endpoint:

38. The following bullet point items have been added to Protocol Summary, Exploratory Objectives, and to Section 3.3, Exploratory Objectives, to add one new exploratory objective:

    7. To explore alternative markers of adherence

39. The following bullet point items have been added to Protocol Summary, Exploratory Endpoints, to add the new exploratory objective endpoints:

    7. Exploration of alternative markers of adherence
    - **Hair dapivirine levels**
    - **Self-reported product use**

40. The following table sub-section has been added to; Section 7.4.1, Months 1 and 2, Table 7, Follow-up Visits, Months 1 and 2; Section 7.4.2, Quarterly Visits (Months 3, 6, 9), Table 8, Quarterly Visits; Section 7.4.3, Product Use End Visit (PUEV), Table 9, PUEV, Month 12; and Section 7.4.4, Study Exit/Termination Visit, Table 10, Study Exit/Termination Visit, to include hair collection as a procedure at each visit:

Hair	• **Collect hair** – **Hair sample for DPV testing and archive**

41. The following table sub-section has been added to Appendix I, Schedule of Study Visits and Evaluations to include hair collection as a procedure at each visit:

		SCR	ENR	M. 1 and 2	Quarterly Visits	PUEV	Study Exit/ Term. Visit (~ 1 Month after the PUEV)
HAIR	**Hair sample(s) for DPV testing and archive**			**X**	**X**	**X**	**X**

42. The following bullet point has been added to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, at the end of the fourth bullet point list, to include hair collection as a procedure at each visit:

- **You will also be asked to provide a hair sample to see how much dapivirine is being absorbed by your body. If you choose not to provide a hair sample, you can still participate in all other study activities. We will reconfirm the decision you make today at all study visits should you change your mind about hair collection.**

43. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), Consent for Storage and Future Testing of Specimens, first, second, seventh and eighth sentences, to include hair samples in the list of specimen samples that may undergo further testing if any are left over after all MTN-025 related testing is completed:

blood, **hair,** vaginal fluid and cervical fluid samples

The following revisions (#44-45) have been made to update the risks associated with the vaginal ring

44. The following revision has been made to Section 13.4.1, Risks, General Subsection, fifth paragraph replaced to update the risks associated with DPV VR use:

~~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~~

~~Please note: Study product risks will be updated when the safety and effectiveness data from ASPIRE are available.~~
Safety data were evaluated from two Phase 3 trials, MTN-020 (ASPIRE) and IPM 027 (The Ring Study), which enrolled a total of 4588 women, and results were reported in February 2016. No safety concerns were noted in DPV VR users as compared to placebo VR users.

45. The following revision has been made to Appendix V, Sample Informed Consent Document (Enrollment), Risks of Study Drugs has been removed as the risks associated with the Study Rings is now sufficient:

~~**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~~

The following revisions (#46-52) have been made to remove the protocol requirement to use FDA-approved HIV testing kits for HIV infection confirmation and to allow for post-infection/pre-seroconversion testing of plasma samples.

46. Instances of "HIV seroconversion" have been changed to "HIV infection" in cases where it is associated with the new HIV testing methods. This change impacts Section 6.4.4, Retrieval of Study Product, second sentence of first paragraph; Section 6.4.4, Retrieval of Study Product, Table 4, Retrieval of Study Product, first and second bullets; Section 6.4.4, Retrieval of Study Product, fourth paragraph; and Section 10.8, Analysis of Secondary Endpoints, first sentence in the first paragraph.

47. The following revisions have been made to Section 7.2, Screening Visit, Table 5, Screening Visit; Section 7.3, Enrollment Visit (Day 0), Table 6, Enrollment Visit (Day 0); Section 7.4.1, Months 1 and 2, Table 7, Follow-up Visits, Months 1 and 2; Section 7.4.2, Quarterly Visits (Months 3, 6, 9), Table 8, Quarterly Visits; Section 7.4.3, Product Use End Visit (PUEV), Table 9, PUEV, Month 12; Section 7.4.4, Study Exit/Termination Visit, Table 10, Study Exit/Termination Visit; and Appendix I, Schedule of Study Visits and Evaluations:

Blood	– HIV-1 **testing**~~serology~~

48. The following revisions have been made to Section 7.6.1, Participants Who Become Infected with HIV, after the second sentence in the first paragraph:

    Participants are offered enrollment in MTN-015 (http://www.mtnstopshiv.org/studies) at the visit when **HIV testing** ~~seroconversion~~ confirmation ~~test~~ results are discussed with the participant.

    For those participants who choose to be maintained in MTN-025 follow-up, regardless of co-enrollment in MTN-015, protocol-specified procedures for MTN-025 will continue, except the following:

    - HIV **testing**~~serology~~, HIV pre- and post-test counseling

49. The following revisions have been made to Section 7.6.1, Participants Who Become Infected with HIV, second and third bullets in last bullet point list:

    - Plasma collection, CD4+ T cell count and HIV-1 RNA PCR will be performed at the clinic visit immediately following confirmation of an HIV-infection and every ~~three months~~ **scheduled visit** thereafter for the remaining follow-up period, or as indicated
    - HIV-1 Genotyping (standard resistance testing) will be performed on the stored plasma closest to the time of ~~confirmed~~ HIV-1 infection**.**
    - ~~It~~**HIV-1 RNA PCR or HIV-1 genotyping** may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center.

50. The following revision has been made to Section 7.6.4, Interim Visits, fifth bullet in bullet point list:

    - For interim HIV counseling and testing in response to participant report of symptoms consistent with acute **HIV infection**~~seroconversion~~ or presumed exposure to HIV

51. The following revision has been made to Section 7.11, Laboratory Evaluations, Local Laboratory sub-section, fourth bullet point in second bullet point list (Blood):

    – HIV **testing**~~serology~~

52. The following revisions have been made to Section 7.12, HIV Infection (Secondary Endpoint) Determination, after the fourth sentence in the first paragraph:

    ~~All confirmatory testing is performed using FDA-approved test kits.~~
    […]
    - The MTN LC will test Study Entry, PUEV, and scheduled Termination Visit specimens from a 10% random sample of participants enrolled at each site for evidence of HIV infection ~~using FDA-licensed tests~~. […]

- The MTN LC will test **plasma specimens collected at** the Study Entry **visit** and **the visit at which HIV infection was detected** ~~Seroconversion specimens~~ from all study participants identified by the local laboratories as having become infected with HIV during the study follow-up period. The LC will also test matched Study Entry and Follow-Up specimens from a random sample of uninfected participants (equal to the number of **infected participants**~~seroconversions~~). Study Entry specimens are collected at participants' Enrollment Visit. ~~Seroconversion~~**Post-infection** specimens are collected at the schedule specified in Section 7.6.1. ~~All specimens will be tested for evidence of HIV infection using FDA-licensed tests.~~ For all **HIV-infected participants**~~seroconverters~~, Study Entry specimens also will be confirmed.

The following revisions (#53-54) have been made to accommodate for plasma sampling at follow-up Months 1 and 2 for DPV testing and archive.

53. The following text has been added to Section 7.4.1, Months 1 and 2, Table 7, Follow-up Visits, Months 1 and 2, under "Laboratory-Blood" component, to include collection of plasma for archive at Months 1 and 2:

Blood	– **Plasma sample for DPV testing and archive**

54. The following revision has been made to Appendix I, Schedule of Study Visits and Evaluations, fifth row in the "Laboratory-Blood" section and superscript legend, to include collection of plasma for archive at Months 1 and 2:

	SCR	ENR	M. 1 and 2	Quarterly Visits	PUEV	Study Exit/ Term. Visit (~ 1 Month after the PUEV)
Plasma sample for DPV testing and archive		◊	**X**	X	X	X

*X mandatory, *If indicated, ŦPer local standard of care, ◊* ***For archive***

The following revisions (#55-56) have been made to make clear that oral tenofovir-based PrEP concomitant use is permitted in countries where it is available:

55. The following revisions have been made to Section 2.7.2, Incorporating Emergent Effective HIV-1 Prevention Strategies, to allow the use of oral Truvada for PrEP by participants in countries where it is licensed for that use:

~~As of June 2014, the United States was the only country where ARVs (the combination daily oral pill emtricitabine/tenofovir disoproxil fumarate [Truvada®]) are licensed for use as pre-exposure prophylaxis (PrEP). However, as candidate microbicides continue to demonstrate evidence of efficacy, the potential for one or more licensed HIV-1 prevention strategies in sub-Saharan Africa may soon become a reality.~~ The HOPE Protocol Team will follow all relevant national policies regarding HIV-1 prevention ~~and will actively consult with stakeholders in the event that an effective intervention is approved locally~~. **In study countries where oral tenofovir-based ARVs are provided to participants by a health care worker as PrEP, use will be documented as a concomitant medication.** Consultation with target populations, policy makers, governments and other stakeholders will be ~~ongoing~~ **conducted as needed** throughout the duration of study implementation and participant follow-up by study leadership, Microbicide Trial Network (MTN) Leadership and the MTN Community Working Group (CWG) **as other products become available**.

56. The following sentence has been added to Section 6.5, Concomitant Medications, after the second sentence, to allow the use of oral Truvada for PrEP by participants in countries where it is licensed for that use:

Oral tenofovir-based ARV use is permitted if approved, available, and provided to participants by a health care provider as PrEP. Oral tenofovir-based ARV use will be documented as a concomitant medication.

The following revisions (#57-61) have been made to accommodate the planned method of data management of the audio files and transcription of these files:

57. Section 11.1, Data Management Responsibilities, second paragraph, has been revised to allow the use of audio files as source documents for in-depth interview data:

~~Transcriptions of il~~Interview~~s~~ **and group discussion files (if applicable)** ~~will be~~ generated in the field ~~and~~**will be** electronically transferred to RTI International using a secure File Transfer Protocol (FTP) site, where they will be

uploaded and managed using a qualitative software package. RTI International will act as a hub, and manage all data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. ~~Original language and translated t~~**Transcripts** will be transferred to RTI International as they are completed. RTI International will save all versions of all files on a secure, password-protected server.

58. Section 11.2, Source Documents and Access to Source Data/Documents, fourth paragraph, has been deleted to allow the use of audio files as source documents for in-depth interview data:

    ~~Audio files will be transcribed and immediately destroyed following a transcription quality assurance check. The site IoR or designee will be responsible for ensuring that these files have been destroyed.~~

59. Section 13.6, Participant Confidentiality, eighth and ninth sentence in the second paragraph, has been revised to allow the use of audio files as source documents for in-depth interview data:

    Audio files will be **translated and** transcribed **in English and securely stored**. Please see SSP **Manual** for guidance ~~regarding audio file destruction~~.

60. Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study?, In-depth Interview(s) and Group Discussions, third sentence of the third paragraph, has been deleted to allow the use of audio files as source documents for in-depth interview data:

    ~~The voice recordings will be destroyed as soon as the audio recording has been typed and checked.~~

61. Appendix VI, Sample Informed Consent Document (MTN-025 Decliner Population), Risks and/or Discomforts, last two sentences of the second paragraph, have been deleted to allow the use of audio files as source documents for in-depth interview data:

    ~~When the information on the audio recording is typed onto paper and fully checked, the recording will be destroyed. Study leaders will make sure this happens.~~

    Additional minor modifications include:

62. List of Abbreviations and Acronyms has been revised to include the acronym for NIAID's Clinical Research Management System, CRMS:

CRMS	**Clinical Research Management System**

63. Throughout the protocol the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events was updated from Version 1.0, December 2004 (Clarification dated August 2009) to Version 2.0, November 2014.

64. Protocol Team Roster- Updates: MTN Leadership and Operations Center (LOC) Protocol Development Manager's name has been updated to Beth Galaska. Jennifer M. Berthiaume's title has been updated to Clinical Data Manager. Danielle Crida's telephone number has been updated to +27-21-6505873

65. Protocol Team Roster- Removals: Arendevi Pather, Patrick Ndase, Karen Patterson, Cynthia Grossman, Katie Schwartz, Flavia Matovu Kiweewa.

66. Protocol Team Roster- Additions:

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67. Section 7.1, Pre-Screening a new fourth sentence has been added to include the planned collection of reasons former MTN-020 (ASPIRE) participants do not enroll in MTN-025 (HOPE).

    […] Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at the study site in the absence of written informed consent from potential participants, provided the information is collected in such a manner that it cannot be linked to potential participant identifiers. **Reason(s) for not enrolling former MTN-020 (ASPIRE) participants (e.g., unable to contact, ineligible based upon pre-screen, associated reasons for ineligibility, refusal, etc.) will be recorded.** At each site, procedures and documentation will comply with local IRB/EC requirements.

68. Section 7.6.1, Participants Who Become Infected with HIV, three bullets have been added after the fourth bullet following the second paragraph, to include plasma, hair and vaginal fluid collection in the list of procedures that would stop in the event of HIV seroconversion during the study:

    - **Plasma collection for DPV testing and storage**
    - **Hair collection**
    - **Vaginal fluid collection**

69. Section 8.1, Safety Monitoring, has been updated to clarify the composition of the PSRT:

    A sub-group of the Protocol Team, including the Protocol Co-Chairs, DAIDS Medical Officer, Protocol Safety Physician(s), **and** IPM Representative ~~and SDMC Clinical Affairs Safety Associate~~ will serve as the Protocol Safety Review Team (PSRT).

70. Section 8.2, Clinical Data Safety Review, has been updated to remove the Clinical Affairs staff designation:

    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.

71. Section 8.3.1, Adverse Events, has been updated to remove the mention of the DataFax system:

    All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the exit visit, the status/outcome of the AE should be updated to "continuing at the end of study participation" ~~and the AE log form should be re-faxed to SCHARP DataFax~~.

72. Section 8.4.1, Adverse Event Reporting to DAIDS, has been revised to update the DAERS support contact information in case of DAERS-related queries, and to correct a number of acronym errors:

    Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/. For each study participant, ~~expedited~~ **E**AE reporting will be undertaken throughout the scheduled duration of follow-up, i.e., from the time of Enrollment through study termination.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for ~~expedited~~ **E**AE reporting to DAIDS. In the event of system outages or technical difficulties, ~~expedited~~ **E**AEs may be submitted via the DAIDS EAE Form. **This form is available on the RSC website, http://rsc.tech-res.com/safetyandpharmacovigilance/.**

For questions about DAERS, please contact **NIAID Clinical Research Management System (CRMS) Support**~~DAIDS ES~~ at ~~DAIDS-ESSupport@niaid.nih.gov~~ **CRMSSupport@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~~ **E**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).

73. Section 11.1, Data Management Responsibilities, has been updated to remove the mention of the DataFax system:

    Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study 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. Study CRF data are transferred to the MTN SDMC, entered, and cleaned using the ~~DataFax~~ data management system.

74. The following revisions have been made to Appendix IV, Sample Informed Consent Document (Screening), Informed Consent section, second to last sentence of first paragraph; and to Appendix V, Sample Informed Consent Document (Enrollment), Informed Consent section, second to last sentence of first paragraph:

    A total of 2629 women enrolled into MTN-020 (ASPIRE) ~~and all former ASPIRE participants who are eligible for MTN-025 (HOPE) may take part~~. It is anticipated that approximately 1000 to 2500 ~~former ASPIRE~~ **eligible** participants will enroll in HOPE.

75. The following revisions have been made to Appendix VI, Sample Informed Consent Document (MTN-025 Decliner Population), Study Procedures sub-section, new third sentence was added to highlight that the in-depth Interviews are planned with a subset of participants only:

    STUDY PROCEDURES
    […] If you agree to take part in this study, the interviewer will ask you some brief questions and write your responses on a form. **It is important you know that not all participants will take part in the IDI; most participants will complete a questionnaire only.** Multiple visits may be needed to complete the IDI and questionnaire(s). During the IDI, the interviewer will also ask in-depth questions, during which time notes may be taken and the conversation will be audio-recorded.

The above information will be incorporated into the next version of the protocol at a later time if it is amended.

LETTER OF AMENDMENT #02 TO:

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

Version 2.0, dated 16 December 2014

DAIDS Protocol #11985
IND #108,743

Date of Letter of Amendment: 28 March 2018

Site Instruction

The following information impacts the MTN-025 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation. The following information impacts the sample informed consent. Your IRB/EC will be responsible for determining the process of informing participants of the contents of this Letter of Amendment (LoA).

Implementation

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. DAIDS sites are still required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). DAIDS sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

Summary of Revisions

This LoA does not impact the overall design or the study visit schedule for MTN-025. The primary purpose of this LoA is to include language allowing international regulatory authority review of study records in both the protocol and informed consent. This LoA also clarifies data management and documentation storage language for the in-depth interview (IDI) and focus group discussion (FGD) source data/documents, updates the Investigator Signature Page, corrects an inconsistency by copying the Exploratory Endpoints previously listed only in the Protocol Summary into Section 4 of the protocol, incorporates the protocol document changes made with Clarification Memos (CM) #1 and #2, updates the Protocol Team Roster, and makes other minor revisions to the protocol.

Unless otherwise noted, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions

The following revisions (#1-6) allow international regulatory authority review of study records:

1. Section 12, Clinical Site Monitoring, last paragraph, second sentence:

   The IoR/designee will also allow inspection of all study-related documentation by authorized representatives of the MTN LOC, SDMC, and LC; NIAID, FDA, IPM, OHRP**, IRBs/ECs,** and **other** local**,** ~~and~~ US**, or international** regulatory authorities.

2. Section 13.1, Institutional Review Boards/Ethics Committees, first paragraph, last sentence:

   ~~The~~ IoR**s/designees** will permit audits by the NIH, IPM, the FDA, OHRP, **MTN LOC, IRBs/ECs, SDMC, and other local, US, or international regulatory authorities,** or any of their appointed agents.

3. Section 13.6, Participant Confidentiality, first bullet point:

   Representatives of the US Federal Government, including the US FDA, the US OHRP, NIH, and/or contractors of the NIH, and other local**,** ~~and~~ US**, or international** regulatory authorities

4. Appendix IV, Sample Informed Consent Document (Screening), Confidentiality, second bullet point:

   Other local, US, or international regulatory authorities [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]

5. Appendix V, Sample Informed Consent Document (Enrollment), Confidentiality, second bullet point:

   Other local, US, or international regulatory authorities [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]

6. Appendix VI, Sample Informed Consent Document (MTN-025 Decliner Population), Confidentiality, second bullet point:

   Other local, US, or international regulatory authorities [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]

The following revisions (#7-9) clarify/specify data management and documentation storage for the IDI and FGD source data, including audio recordings:

7. Section 11.1, Data Management Responsibilities, second paragraph, first sentence, has been revised to describe the source data management process and to explicitly list which documents will be considered as source data for the qualitative behavioral evaluations (i.e., IDIs and FGDs):

   Transcriptions of interviews ~~Interview~~ and group discussion**s** ~~files~~ (if applicable) **will be** generated **using the audio recordings. Both the audio recordings and the transcripts** ~~in the field~~ will be electronically transferred to RTI International using a secure File Transfer Protocol (FTP) site, where they will be uploaded and managed using a qualitative software package. **Interview and group discussion notes (if applicable) will be kept at the site in the participant files. The qualitative data from MTN-025 will include three main data sources: original handwritten notes of IDIs and FGDs, audio-recorded IDIs and FGDs, and transcripts of IDIs and FGDs.**

8. Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study?, In-depth Interview(s) and Group Discussions, third paragraph, fifth sentence has been revised and last sentence has been added, to explicitly include audio recordings as one of the documents considered to be source data and to disclose to participants how long the audio recordings will be stored:

   Your audio recordings and any other ~~The~~ information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-025(HOPE) study team for the purposes of this research. ***[Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/IECs:*** **The audio recordings, notes, and transcripts from these materials will be kept for at least two years after the vaginal ring is approved for marketing or two years after all developmental research on the vaginal ring is stopped.]**

9. Appendix VI, Sample Informed Consent Document (MTN-025 Decliner Population), Risks and/or Discomforts, second paragraph, last sentence, has been added to explicitly disclose to participants how long the audio recordings will be stored:

   [Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/IECs: **The audio recordings, notes, and transcripts from these materials will be kept for at least two years after the vaginal ring is approved for marketing or two years after all developmental research on the vaginal ring is stopped.]**

The following revision updates the Investigator Signature Form language describing the investigators' responsibilities as per DAIDS requirements (see Appendix at the end of this LoA for the updated Investigator Signature Form):

10. Investigator Signature Form, first paragraph:

    I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol **and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference for Harmonization Guideline for Good Clinical Practice**

(E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., NIH, DAIDS) and institutional policies. ~~I 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.~~

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

The following revision corrects an inconsistency by copying the Exploratory Endpoints previously listed only in the Protocol Summary into Section 4, Study Design, as per our usual practice:

11. Section 4.2, Summary of Major Endpoints, after Secondary Endpoints:

Exploratory Endpoints:

1. **Understanding of efficacy**
   - **Self-reported understanding of partial efficacy**

2. **Understanding of ring acceptability in the context of known efficacy**
   - **Self-reported product acceptability and attitudes towards combination prevention**

3. **Feasibility:**
   - **Participant report of product storage issues and feasibility regarding the follow-up schedule**
   - **Visit retention**
   - **Proportion of returned rings (used and unused)**

4. **Genital microenvironment**
   - **In genital swab samples, candidate biomarkers of safety, adherence and efficacy, HIV exposure and antiretroviral resistance, and genital microflora**

5. **Characterization of MTN-020 participants who do not enroll in MTN-025**
   - **Participant report of the factors that led to her decision to decline enrollment into MTN-025**

6. **Characterization of MTN-020 participants who do not accept study product in MTN-025**
   - **Participant report of the factors that led to her decision to not accept study product**

7. **Exploration of alternative markers of adherence**
   - **Hair dapivirine levels**
   - **Self-reported product use**

The following revisions (#12-17) update the URLs where current DAIDS guidance documents can be found:

12. Section 7.13, Specimen Collection and Processing:

Each study site will adhere to the standards of good clinical laboratory practice (https://www.niaid.nih.gov/sites/default/files/~~documents/~~gclp.pdf)

13. Section 7.14, Specimen Handling:

Specimens will be handled in accordance with current requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials. ~~(https://www.niaid.nih.gov/sites/default/files/documents/laboratorypolicy1.pdf)~~ **~~(~~https://www.niaid.nih.gov/research/daids-clinical-research-policies-us-labs**~~)~~**

14. Section 8.4.1, Adverse Event Reporting to DAIDS:

    In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the RSC website, http://rsc.tech-res.com/clinical-research-sites/safety-reporting/~~daids~~**daers**/paper-eae-reporting.

15. Section 11.2, Source Documents and Access to Source Data/Documents:

    All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/~~documents/~~daids-sourcedocpolicy.pdf) and the relevant appendix regarding source documentation (https://www.niaid.nih.gov/sites/default/files/~~documents/~~sourcedocappndx.pdf).

16. Section 11.3, Quality Control and Quality Assurance:

    All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites (https://www.niaid.nih.gov/sites/default/files/~~documents/~~qmppolicy.pdf).

17. Section 13.5, Informed Consent Process:

    Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/~~documents/~~daids-sourcedocpolicy.pdf).

The following revisions (#18-21) incorporate the changes to protocol text made with CM #1:

18. Section 7.3, Enrollment Visit (Day 0): Table 6, Enrollment Visit has been modified to correct the omission of an asterisk indicating that the insertion of one study vaginal ring at the Enrollment Visit is an "if indicated" procedure, see bolded text below:

Table 6: Enrollment Visit

Study Product/Supplies	• Offer condoms • Provision of study VR use instructions* • Offer and, if accepted, provide study VR(s) • Insertion of one study VR***** • Digital exam by clinician to check VR placement*

19. Section 7.11, Laboratory Evaluations, has been modified to add language at the end of the section regarding hair collection for consistency with similar language elsewhere in the protocol and consent forms:

    IPM or MTN Designated Laborator**ies**~~y~~:
    - Study Product- Vaginal Ring
      - Adherence assessment(s)
    - **Hair for biomarkers and archive**

20. Section 7.13, Specimen Collection and Processing, has been modified to update the URL where the current DAIDS standards of good clinical laboratory practice can be found:

    Each study site will adhere to the standards of good clinical laboratory practice ~~(http://apps.who.int/tdr/publications/tdr-research-publications/gclp-web/pdf/gclp-web.pdf)~~
    (https://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gclp.pdf)

21. Section 7.14, Specimen Handling, has been modified to update the URL where the current DAIDS Laboratory Policy can be found:

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)~~**(https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx)**

The following revisions (#22-26) incorporate the changes to protocol text made with CM #2:

22. The following modifications were made to delete language related to cervical fluid collection that remained in the protocol text due to an administrative error, as there are no cervical fluid samples being collected for research purposes in this study:

    a) Appendix V: Sample Informed Consent Document (Enrollment), *What Do I Have to Do if I Decide to Take Part in the MTN-025 Study?*:

    - Provide vaginal fluid ~~and cervical fluid~~ samples:
      - To see how the dapivirine vaginal ring protects against HIV and to explore the health of the female genital tract. The vaginal fluid ~~and cervical fluid~~ collected will be used for research purposes only.

    b) Appendix V: Sample Informed Consent Document (Enrollment), *Consent for Storage and Future Testing of Specimens*:

    There might be a small amount of blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your leftover blood, hair, **and** vaginal fluid~~, and cervical fluid~~ samples, and related health information for use in future studies… You can still enroll in this study if you decide not to have leftover blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples stored for future studies. If you do not want the left-over blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples stored, we will destroy these left over specimens.

23. The following modifications were made to Section 6.4.2, Study Product Dispensing, to clarify that the IoR designee can also use their discretion to provide additional rings to participants unable to attend their next scheduled visit:

    If the participant is unable to attend her next scheduled visit an additional ring(s) may be provided at the discretion of the IoR**/designee** as permitted in the SSP…

    … If a participant requires an additional ring for any reason, at a time other than when she is scheduled to receive one, additional product may be dispensed at the discretion of the IoR**/designee**.

24. The following modifications were made to clarify that hair sampling procedures are optional at each study visit, to be consistent with hair sampling language in the sample informed consent:

    a) Tables in Section 7.4.1 – Months 1 and 2, Section 7.4.2 – Quarterly Visits (Months 3, 6, 9), Section 7.4.3 – Product Use End Visit (PUEV), and Section 7.4.4 – Study Exit/Termination Visit, only row under "Hair":

    - Collect hair **(required unless participant declines)**

    b) Appendix I, Schedule of Study Visits and Evaluations, only row under "Hair":

    Hair sample(s) for DPV testing and archive **(required unless participant declines)**

25. The following modifications were made to Section 11.1, Data Management Responsibilities, to explicitly state that the overall data management system used in this study adheres to the US-EU Safe Harbor requirements and the EU Data Protection Directive 95/46/EC and is both ICH GCP and CFR compliant, along with a note clarifying how paperless data collection is being rolled out in the HOPE study:

    Study CRF data are **entered into the MTN-025 database,** transferred **in compliance with the US-EU Safe Harbor Requirements and the EU Data Protection Directive 95/46/EC** to the MTN SDMC, ~~entered,~~ and cleaned using **Medidata Rave, a**~~the~~ data management system **compliant with the International Council on Harmonization (ICH) Good Clinical Practices (GCP) and US CFR guidelines for electronic data capture**.

26. The following modifications were made to update the URLs where current DAIDS guidance documents can be found:

a) Section 7.13, Specimen Collection and Processing:

Each study site will adhere to the standards of good clinical laboratory practice ~~(https://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gclp.pdf)~~ **(https://www.niaid.nih.gov/sites/default/files/documents/gclp.pdf)**

b) Section 7.14, Specimen Handling:

Specimens will be handled in accordance with current requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials. ~~(https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx)~~ **(https://www.niaid.nih.gov/sites/default/files/documents/laboratorypolicy1.pdf)**

c) Section 8.4.1, Adverse Event Reporting to DAIDS:

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

d) Section 8.4.1, Adverse Event Reporting to DAIDS:

In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the RSC website, ~~http://rsc.tech-res.com/safetyandpharmacovigilance/~~**http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting**.

e) Section 8.4.3, Grading Severity of Events:

The most current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014 [Dated November 2007]), will be used and is available on the RSC website at ~~http://rsc.tech-res.com/safetyandpharmacovigilance/~~**http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables**.

f) Section 11.2, Source Documents and Access to Source Data/Documents:

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials ~~(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocpolicy.pdf)~~**(https://www.niaid.nih.gov/sites/default/files/documents/daids-sourcedocpolicy.pdf)** and the relevant appendix regarding source documentation ~~(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocappndx.pdf)~~**(https://www.niaid.nih.gov/sites/default/files/documents/sourcedocappndx.pdf)**.

g) Section 11.3, Quality Control and Quality Assurance:

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites ~~(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdfhttp://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdf)~~**(https://www.niaid.nih.gov/sites/default/files/documents/qmppolicy.pdf)**.

h) Section 13.5, Informed Consent Process:

Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials ~~(http://rsc.tech-res.com/policiesandregulations/)~~**(https://www.niaid.nih.gov/sites/default/files/documents/daids-sourcedocpolicy.pdf)**.

Additional minor modifications include:

27. Protocol Team Roster- Updates, including those made with CM #1:

    a) From CM #1:
        - Gonasagrie Nair will be Site Investigator of Record for the Cape Town Emavundleni CRS instead of the CAPRISA eThekwini CRS.
        - Logashvari Naidoo will be Site Investigator of Record for the MRC-Chatsworth CRS instead of the MRC-Tongaat CRS.
        - Zip codes for all US NIH protocol team roster members changed from 20892 to 20852.
        - Addresses for all MTN LOC – FHI 360 protocol team roster members edited to add FHI 360 and remove P.O. Box 21059.
        - Ashley Mayo's title changed to Sr. Clinical Research Manager.
        - MRC CTU Site Investigator titles for Zakir Gaffoor, Nitesha Jeenarain and Samantha Siva changed to CRS Leader.

    b) Current updates:
        - Vimla Naicker will be Site Investigator of Record for the MRC-Tongaat CRS and the MRC-Verulam CRS instead of the MRC-Botha's Hill CRS.
        - Zakir Gaffoor will be CRS Leader for the MRC-Verulam CRS instead of the MRC-Chatsworth CRS.
        - Nitesha Jeenarain will be CRS Leader for the MRC-Chatsworth CRS instead of the MRC-Verulam CRS.
        - The name of the University of Zimbabwe-University of California San Francisco Collaborative Research Program (UZ-UCSF) Clinical Trials Unit was changed to University of Zimbabwe College of Health Sciences Clinical Research Centre (UZCHS-CTRC).
        - Email addresses for all UZCHS-CTRC protocol team roster members edited to change @uz-ucsf.co.zw to @uzchs-ctu.org.
        - Luis Duran's title changed to Project Manager.
        - Devika Singh's address was changed to 19 Randall Drive, Jericho, VT 05465 USA, her phone number was changed to 206-920-0975, and her fax number was removed.

28. Protocol Team Roster- Removals, including those made with CMs #1 and #2:

    a) From CM #1: Danielle Crida, Newton Kumwenda, Jeffrey Stringer, Vaneshree Govender, Beth Galaska, Kailazarid Gomez, and Fatima Glyn Zulu.

    b) From CM #2: Ken Ho, Ian McGowan.

    c) Current removals: Arendevi Pather, Anamika Premrajh, Nishanta Singh, Francis Martinson, Ellen Conser, Jennifer Berthiaume.

29. Protocol Team Roster- Additions, including those made with CM #1:

    a) From CM #1:

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b) Current additions:

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The above information will be incorporated into the next version of the protocol at a later time if it is amended.

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

INVESTIGATOR SIGNATURE FORM

Version 2.0; December 16, 2014
Letter of Amendment #01; April 11, 2016
Letter of Amendment #02; March 28, 2018

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) (DAIDS Protocol ID: 11985)

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

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

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

_____
Name of Investigator of Record

_____ _____
Signature of Investigator of Record Date

Microbicide Trials Network

CLARIFICATION MEMO #01 TO:

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

DAIDS Protocol #: 11985

IND#: 108,743

Version 2.0 / 16 December 2014
Letter of Amendment #01 / 11 April 2016

Clarification Memo Date: 5 August 2016

Section 1: Summary of Clarifications and Rationale

The procedures clarified in this Clarification Memorandum (CM) have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB approval of this CM is not required by the sponsor; however, investigators may submit the CM to the IRB overseeing the study at their site for information. This CM is official MTN-025 documentation and is effective immediately. A copy of this CM must be retained in each study site's Essential Documents file for MTN-025. No change in informed consent is necessitated by or included in this CM.

This document clarifies language regarding the insertion of one study vaginal ring at the Enrollment Visit, and adds language to the laboratory section for consistency with other protocol and consent language regarding hair specimen collection. Additionally, this document updates the location of DAIDS laboratory policy and guidance documentation, and the Protocol Team Roster.

Section 2: Implementation

With the exception of updates to the protocol team roster, text to be deleted is noted below with a ~~strikethrough~~ and text to be added is in **bold.**

1.) Section 7.3, *Enrollment Visit (Day 0)*: Table 6, *Enrollment Visit* has been modified to correct the omission of an asterisk indicating that the insertion of one study vaginal ring at the Enrollment Visit is an "if indicated" procedure, see bolded text below:

Table 6: Enrollment Visit

Study Product/Supplies	• Offer condoms • Provision of study VR use instructions* • Offer and, if accepted, provide study VR(s) • Insertion of one study VR* • Digital exam by clinician to check VR placement*

2.) Section 7.11, Laboratory Evaluations, has been modified to add language at the end of the section regarding hair collection for consistency with similar language elsewhere in the protocol and consent forms.

IPM or MTN Designated Laborator**ies**~~y~~:

- Study Product- Vaginal Ring
  - Adherence assessment(s)

- **Hair for biomarkers and archive**

3.) Section 7.13, *Specimen Collection and Processing*, has been modified to update the URL where the current DAIDS standards of good clinical laboratory practice can be found.

Each study site will adhere to the standards of good clinical laboratory practice ~~(http://apps.who.int/tdr/publications/tdr-research-publications/gclp-web/pdf/gclp-web.pdf)~~ **(https://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gclp.pdf)**

4.) Section 7.14, *Specimen Handling*, has been modified to update the URL where the current DAIDS Laboratory Policy can be found.

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)~~ **(https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx)**

5.) Protocol Team Roster-Updates:

a) Gonasagrie Nair will be Site Investigator of Record for the Cape Town Emavundleni CRS instead of the CAPRISA eThekwini CRS.

b) Logashvari Naidoo will be Site Investigator of Record for the MRC-Chatsworth CRS instead of the MRC-Tongaat CRS.

c) Zip codes for all US NIH protocol team roster members changed from 20892 to 20852.

d) Addresses for all MTN LOC – FHI 360 protocol team roster members edited to add FHI 360 and remove P.O. Box 21059.

e) Ashley Mayo's title changed to Sr. Clinical Research Manager.

f) MRC CTU Site Investigator titles for Zakir Gaffoor, Nitesha Jeenarain and Samantha Siva changed to CRS Leader.

6.) Protocol Team Roster- Removals: Danielle Crida, Newton Kumwenda, Jeffrey Stringer, Vaneshree Govender, Beth Galaska, Kailazarid Gomez, and Fatima Glyn Zulu.

7.) Protocol Team Roster- Additions:

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The above information will be incorporated into the next version of the protocol at a later time if it is amended.

Microbicide Trials Network

CLARIFICATION MEMO #02 TO:

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

DAIDS Protocol #: 11985

IND#: 108,743

Version 2.0 / 16 December 2014
Letter of Amendment #01 / 11 April 2016

Clarification Memo Date: 11 November 2016

Section 1: Summary of Clarifications and Rationale

The procedures clarified in this Clarification Memorandum (CM) have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB/IEC approval of this CM is not required by the sponsor; however, investigators may submit the CM to the IRB/IEC overseeing the study at their site for information. This CM is official MTN-025 documentation and is effective immediately. A copy of this CM must be retained in each study site's Essential Documents file for MTN-025. No change in informed consent is necessitated by or included in this CM.

This document clarifies the intent of one of the exclusion criteria in the context of an open-label follow-on trial to explicitly allow former MTN-020(ASPIRE) participants who have moved since ASPIRE and/or who plan to move or travel during MTN-025(HOPE) to enroll in HOPE. This document also deletes language related to cervical fluid collection from the sample informed consent, which was left in the informed consent text due to an administrative error, clarifies product dispensation and hair sampling language for consistency, and clarifies that the data management system utilized is compliant with US-EU Safe Harbor, the EU Data Protection Directive 95/46/EC, ICH GCP and CFR requirements. Additionally, this document updates the location of DAIDS policy and guidance documentation, and the Protocol Team Roster.

Section 2: Implementation

With the exception of updates to the protocol team roster, text to be deleted is noted below with a ~~strikethrough~~, text to be added is in **bold**, and text in ***bold italics*** is not to be added, but to serve as a clarification of the implementation item in question. This information will be included in the protocol the next time the protocol is updated.

1.) The following refers to Section 5.3, *Exclusion Criteria,* and clarifies the intent of Exclusion Criteria 2a and 2b in the context of an open-label follow-on trial to explicitly allow enrollment of former ASPIRE participants who have relocated since ASPIRE and/or who plan to relocate or travel during HOPE, but who would otherwise be eligible and willing to participate in HOPE:

The intent of Exclusion Criteria 2a and 2b is to ensure that only study participants who will be able to adhere to their Study Visit schedule are enrolled.

A participant who plans to move away from the MTN-025 study site at which she will be enrolled (i.e., Exclusion Criteria 2a) may still be enrolled if, once she moves, she will have access to another MTN-025 study site and can be transferred to that other site, or if she is willing and able to travel back to her study site to attend study visits.

A participant who plans to travel for more than three months away from the MTN-025 study site at which she will be enrolled (i.e., Exclusion Criteria 2b) may still be enrolled if she is willing and able to travel back to the study site to attend study visits.

Therefore, participants should be excluded from enrollment as per Exclusion Criteria 2a and 2b only if they plan to move away from the study site or they plan to travel away from the study site for more than three months and they are unwilling or unable to travel back to their site to attend study visits and do not have access to any MTN-025 study sites to which they can be transferred for the study.

2.) The following modifications have been made to delete language related to cervical fluid collection that remained in the protocol text due to an administrative error, as there are no cervical fluid samples being collected for research purposes in this study:

a) Appendix V: Sample Informed Consent Document (Enrollment), *What Do I Have to Do if I Decide to Take Part in the MTN-025 Study?*:

- Provide vaginal fluid ~~and cervical fluid~~ samples:
  - To see how the dapivirine vaginal ring protects against HIV and to explore the health of the female genital tract. The vaginal fluid ~~and cervical fluid~~ collected will be used for research purposes only.

b) Appendix V: Sample Informed Consent Document (Enrollment), *Consent for Storage and Future Testing of Specimens*:

There might be a small amount of blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your leftover blood, hair, **and** vaginal fluid~~, and cervical fluid~~ samples, and related health information for use in future studies… You can still enroll in this study if you decide not to have leftover blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples stored for future studies. If you do not want the left-over blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples stored, we will destroy these left over specimens.

3.) The following modifications have been made to Section 6.4.2, Study Product Dispensing, to clarify that the IoR designee can also use their discretion to provide additional rings to participants unable to attend their next scheduled visit:

If the participant is unable to attend her next scheduled visit an additional ring(s) may be provided at the discretion of the IoR**/designee** as permitted in the SSP…

… If a participant requires an additional ring for any reason, at a time other than when she is scheduled to receive one, additional product may be dispensed at the discretion of the IoR**/designee**.

4.) The following modifications have been made to clarify that hair sampling procedures are optional at each study visit, to be consistent with hair sampling language in the sample informed consent:

a) Tables in Section 7.4.1 – Months 1 and 2, Section 7.4.2 – Quarterly Visits (Months 3, 6, 9), Section 7.4.3 – Product Use End Visit (PUEV), and Section 7.4.4 – Study Exit/Termination Visit, only row under "Hair":

- Collect hair **(required unless participant declines)**

b) Appendix I, Schedule of Study Visits and Evaluations, only row under "Hair":

Hair sample(s) for DPV testing and archive **(required unless participant declines)**

5.) The following modifications have been made to Section 11.1, *Data Management Responsibilities*, to explicitly state that the overall data management system used in this study adheres to the US-EU Safe Harbor requirements and the EU Data Protection Directive 95/46/EC and is both ICH GCP and CFR compliant, along with a note clarifying how paperless data collection is being rolled out in the HOPE study:

Study CRF data are **entered into the MTN-025 database,** transferred **in compliance with the US-EU Safe Harbor Requirements and the EU Data Protection Directive 95/46/EC** to the MTN SDMC, ~~entered,~~ and cleaned using **Medidata Rave, a**~~the~~ data management system **compliant with the International Council on Harmonization (ICH) Good Clinical Practices (GCP) and US CFR guidelines for electronic data capture**.

Screening visit CRFs will first be completed in paper format, with data entered into the electronic format CRFs (eCRFs) in the Medidata Rave study database after an enrollment determination has been made for a given participant. The intent is for all other CRFs to be completed in electronic format (paperless) only.

Sites may continue to complete enrollment and follow-up visit CRFs in paper format first, prior to data entry into the study database, until they have completed their transition to paperless eCRF completion in the study database.

6.) The following modifications have been made to update the URLs where current DAIDS guidance documents can be found:

a) Section 7.13, *Specimen Collection and Processing*:

Each study site will adhere to the standards of good clinical laboratory practice ~~(https://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gclp.pdf)~~ **(https://www.niaid.nih.gov/sites/default/files/documents/gclp.pdf)**

b) Section 7.14, *Specimen Handling*, has been modified to update the URL where the current DAIDS Laboratory Policy can be found:

Specimens will be handled in accordance with current requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials. ~~(https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx)~~ **(https://www.niaid.nih.gov/sites/default/files/documents/laboratorypolicy1.pdf)**

c) Section 8.4.1, *Adverse Event Reporting to DAIDS*, has been modified to update the URL where the current DAIDS EAE Manual can be found:

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

d) Section 8.4.1, *Adverse Event Reporting to DAIDS*, has been modified to update the URL where the current DAIDS EAE Form can be found:

In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the RSC website, ~~http://rsc.tech-res.com/safetyandpharmacovigilance/~~**http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting**.

e) Section 8.4.3, *Grading Severity of Events*, has been modified to update the URL where the current DAIDS AE Grading Tables can be found:

The most current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014 [Dated November 2007]), will be used and is available on the RSC website at ~~http://rsc.tech-res.com/safetyandpharmacovigilance/~~**http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables**.

f) Section 11.2, *Source Documents and Access to Source Data/Documents*, has been modified to update the URL where the current Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials policy and appendices can be found:

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials ~~(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocpolicy.pdf)~~**(https://www.niaid.nih.gov/sites/default/files/documents/daids-sourcedocpolicy.pdf)** and the relevant appendix regarding source documentation ~~(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocappndx.pdf)~~**(https://www.niaid.nih.gov/sites/default/files/documents/sourcedocappndx.pdf)**.

g) Section 11.3, *Quality Control and Quality Assurance*, has been modified to update the URL where the current Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites policy can be found:

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites ~~(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdfhttp://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdf)~~**(https://www.niaid.nih.gov/sites/default/files/documents/qmppolicy.pdf)**.

h) Section 13.5, *Informed Consent Process*, has been modified to update the URL where the current Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials policy can be found:

Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials ~~(http://rsc.tech-res.com/policiesandregulations/)~~**(https://www.niaid.nih.gov/sites/default/files/documents/daids-sourcedocpolicy.pdf)**.

7.) Protocol Team Roster- Removals: Ken Ho, Ian McGowan.

The above information will be incorporated into the next version of the protocol at a later time if it is amended.