MTN-020

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women

Microbicide Trials Network

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS v

PROTOCOL TEAM ROSTER viii

INVESTIGATOR SIGNATURE FORM xx

PROTOCOL SUMMARY xxi

1 KEY ROLES 1

1.1 Protocol Identification 1
1.2 Sponsor and Monitor Identification 1
1.3 Medical Officer 1
1.4 Clinical Laboratories 2
1.5 Data Center 2
1.6 Study Operations 2

2 INTRODUCTION 3

2.1 Microbicides and Human Immunodeficiency Virus (HIV) Prevention 3
2.2 Dapivirine Vaginal Ring 6
2.3 Placebo VR 8
2.4 *In vitro* Studies 8
2.5 Condom Compatibility Studies of Dapivirine 9
2.6 Clinical Studies 12
2.7 Study Hypothesis and Rationale for Study Design 18

3 OBJECTIVES 20

3.1 Primary Objectives 20
3.2 Secondary Objectives 20
3.3 Exploratory Objectives 20

4 STUDY DESIGN 20

4.1 Identification of Study Design 20
4.2 Summary of Major Endpoints 21
4.3 Description of Study Population 21
4.4 Time to Complete Accrual 21
4.5 Study Groups 21
4.6 Expected Duration of Participation 21
4.7 Sites 22

5 STUDY POPULATION 22

5.1 Selection of the Study Population 22
5.2 Inclusion Criteria 23
5.3 Exclusion Criteria 24
5.4 Co-enrollment Guidelines 26

6 STUDY PRODUCT 27

6.1 Regimen 27
6.2 Administration 27
6.3 Study Product Formulation 27
6.4 Supply and Accountability 28
6.5 Adherence Counseling and Assessment 30
6.6 Concomitant Medications 30
6.7 Use of Intravaginal Medications and Practices 30

7 STUDY PROCEDURES 31

7.1 Pre-Screening 31
7.2 Screening Visit 31
7.3 Enrollment Visit (Day 0) 33
7.4 Follow-up Visits 34
7.5 Follow-up Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product 37
7.6 Final Contact 40
7.7 Behavioral Evaluations 40
7.8 Clinical Evaluations and Procedures 41
7.9 Laboratory Evaluations 41
7.10 Primary HIV-1 Endpoint Determination 42
7.11 Specimen Collection and Processing 43
7.12 Specimen Handling 43
7.13 Biohazard Containment 44

8 ASSESSMENT OF SAFETY 44

8.1 Safety Monitoring 44
8.2 Adverse Events Definitions and Reporting Requirements 44
8.3 Expedited Adverse Event Reporting Requirements 47
8.4 Social Harms Reporting 48
8.5 Regulatory Requirements 48

9 CLINICAL MANAGEMENT 49

9.1 Grading System 49
9.2 Dose Modification Instructions 49
9.3 General Criteria for Temporary Hold and Permanent Discontinuation of Study Product 49
9.4 Temporary Product Hold/Permanent Discontinuation in Response to Observed Adverse Events 50
9.5 Genital Sexually Transmitted Infection, Reproductive Tract Infection and Other Clinical Findings 51
9.6 HIV-1 Infection 53
9.7 Pregnancy 53
9.8 Criteria for Early Termination of Study Participation 54

10 STATISTICAL CONSIDERATIONS 54

10.1 Overview and Summary of Design 54
10.2 Study Endpoints 55
10.3 Sample Size and Power Calculations 56
10.4 Participant Accrual, Follow-up and Retention 57
10.5 Randomization 58
10.6 Blinding 58

10.7 Data and Safety Monitoring Procedures 58
10.8 Primary Analysis 61
10.9 Analysis of Main Secondary Endpoints 62
10.10 Missing Data 63

11 DATA HANDLING AND RECORDKEEPING 63

11.1 Data Management Responsibilities 63
11.2 Source Documents and Access to Source Data/Documents 64
11.3 Quality Control and Quality Assurance 64

12 CLINICAL SITE MONITORING 64

13 HUMAN SUBJECTS PROTECTIONS 65

13.1 Institutional Review Boards/Ethics Committees 65
13.2 Protocol Registration 65
13.3 Study Coordination 66
13.4 Risk Benefit Statement 66
13.5 Informed Consent Process 68
13.6 Participant Confidentiality 69
13.7 Special Populations 69
13.8 Compensation 70
13.9 Communicable Disease Reporting 70
13.10 Access to HIV-related Care 70
13.11 Study Discontinuation 70

14 PUBLICATION POLICY 71

15 APPENDICES 72

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS 73

APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING- SCREENING/ENROLLMENT 75

APPENDIX III: ALGORITHM FOR HIV ANTIBODY TESTING FOR FOLLOW-UP AND PRIMARY ENDPOINT 76

APPENDIX IV: SAMPLE INFORMED CONSENT DOCUMENT (SCREENING) 77

APPENDIX V: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT) 84

REFERENCES 94

Table of Figures

Figure 1: Projected Enrollment Used for Study Design 57

Table 1: Clinical Phase I/II of Dapivirine Vaginal Rings 14
Table 2: Study Regimen 27
Table 3: Retrieval of Study Product 29
Table 4: Screening Visit 32
Table 5: Enrollment Visit 33
Table 6: Follow-up Visits: Monthly, Quarterly, Semi-Annually 34
Table 7: PUEV 36
Table 8: Study Exit/Termination Visit 37

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
ACASI	Audio Computer-Assisted Self Interviewing
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
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
CNS	central nervous system
CORE	Coordinating and Operations Center
CRF	Case Report Form
CRPMC	Clinical Research Products Management Center
CT	Chlamydia trachomatis
CTA	clinical trial agreement
CWG	Community Working Group
DAERS	DAIDS Adverse Events Reporting System
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAPY	di-aminopyrimidine
DLV	delavirdine
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EAE	expedited adverse event
EC	Ethics Committee
EE	ethinyl estradiol
EFV	efavirenz
ENG	etonogestrel
FACTS	Follow on Africa Consortium for Tenofovir Studies
FDA	Food & Drug Administration (U.S.)
FHCRC	Fred Hutchinson Cancer Research Center
g	grams
GC	*Neisseria gonorrhoeae*
GCP	Good Clinical Practice
GEE	General Estimating Equation
GMP	good manufacturing practices
hCG	human chorionic gonadotropin

HEC	hydroxyethyl cellulose
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
IFA	immunofluorescent assay
IND	Investigational New Drug
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
JHU	Johns Hopkins University
KOH	potassium hydroxide
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantification
µg	microgram
mg	milligram
mL	milliliter
MO	Medical Officer
MOP	Manual of Operational Procedures
MTD	maximum tolerated dose
MTN	Microbicide Trials Network
MU	Makerere University
NAAT	nucleic acid amplification test
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no-observed-adverse-effect-level
NL	Network Laboratory
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OHRP	Office for Human Research Protections
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PID	participant identification number
PK	pharmacokinetic
PMPA	Tenofovir 1% gel
PMTCT	Prevention of Mother-to-Child Transmission
PPD	Pharmaceutical Product Development, Inc.
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
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

SAP	Statistical Analysis Plan
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDMC	Statistical Data Management Center
SHIV	Simian Human Immunodeficiency Virus
SIV	site initiation visit
SMC	Study Monitoring Committee
SSP	study specific procedure(s)
STD	sexually transmitted disease
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
TEAE	treatment emergent adverse event
TPGS	tocopheryl polyethylene glycol succinate
UCSF	University of California- San Francisco
UKZN	University of KwaZulu-Natal
UNAIDS	Joint United Nations Programme on HIV/AIDS
UPMC	University of Pittsburgh Medical Center
USA	United States of America
UTI	urinary tract infection
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VR	vaginal ring
WHO	World Health Organization
wt	wild-type

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INVESTIGATOR SIGNATURE FORM

Version 1.0

September 28, 2011

A Study of the Microbicide Trials Network

Funded by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Mental Health
US National Institutes of Health

IND Holder:
International Partnership for Microbicides

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 Vaginal Matrix Ring Containing Dapivirine 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 the Microbicide Trials Network (MTN) and International Partnership for Microbicides (IPM) policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, NIAIDS, NIH, NIMH, and IPM for review prior to submission.

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

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A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women

PROTOCOL SUMMARY

Short Title: A Study to Prevent Infection with a Ring for Extended Use (ASPIRE)

Clinical Phase: Phase 3

IND Sponsor: International Partnership for Microbicides

Protocol Chair: Jared Baeten, MD, PhD

Protocol Co-chair: Thesla Palanee, PhD

Sample Size: Approximately 3476 women

Study Population: Sexually active HIV-uninfected women, non-pregnant, 18-45 years of age

Study Sites: Sites selected by the MTN Executive Committee

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

Study Duration: Accrual will require approximately 12 months. Each participant will engage in the screening process for up to 4 weeks (28 days) prior to enrollment and will use investigational product until 120 events (HIV-1 seroconversions) are observed in the trial. Based on the statistical assumptions listed below, the targeted number of incident seroconversions is expected to be reached approximately 12 months after the date upon which the last participant enrolls in the trial.

Each participant will have 4 additional weeks of follow-up after ring discontinuation, to identify HIV-1 seroconversions that are not detected during the product-use period.

Study Products:

- Dapivirine Vaginal Ring (VR)
- Placebo VR

Study Regimen: Participants will be randomized in a 1:1 ratio to receive either a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine or a placebo VR

Primary Objectives:

- To determine the *effectiveness* of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks, in preventing HIV-1 infection among healthy sexually active HIV-uninfected women

- To assess the *safety* of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over the investigational product use period

Primary Endpoints:

- **Effectiveness**
  - HIV-1 infection as measured by seroconversion at the end of the investigational product use period with seroconversion defined by the algorithm in Appendix III

- **Safety**
  - Grade 2 adverse events (AEs) judged to be related to study product
  - Grade 3 and 4 AEs
  - All serious adverse events

Secondary Objectives:

- To evaluate the *acceptability* of the study VR (dapivirine or placebo) in HIV-uninfected women, when inserted once every 4 weeks over the investigational product use period

- To evaluate the *adherence* to the study VR (dapivirine or placebo) in HIV-uninfected women, when inserted once every 4 weeks over the investigational product use period

- To assess the frequency of HIV-1 *drug resistance* in women who acquire HIV-1 infection while using the investigational product

- To evaluate the *relationship between drug concentration* and *HIV-1 seroconversion*

Secondary Endpoints:

- **Acceptability**
  - Participant report of participant and partner-related acceptability including (dis)comfort, ring insertion and removal/ expulsion issues, change in sexual feelings, willingness to use in the future

- **Adherence**
  - Frequency of study VR removal/expulsions (voluntary and involuntary) and duration without VR inserted in vagina

- **HIV-1 Drug Resistance**
  - HIV-1 drug resistance mutations among participants who acquire HIV-1 infection

- **Drug Concentration Data**
  - Steady-state drug concentrations in blood and vaginal fluid

Exploratory Objectives:

- Describe changes in the *genital microenvironment*

- To assess *correlation of steady-state drug concentration and adherence measures*

- To assess the *incidence of HIV-1 seroconversion* during 4 weeks off study product, between the product use end visit (PUEV) and termination visit

Exploratory Endpoints:

- **Genital microenvironment changes**
  - Changes in candidate biomarkers of safety and efficacy

- **Correlation of steady-state drug concentration and adherence measures**
  - Adherence measures as outlined above for the secondary objective
  - Steady-state drug concentration

- **Delayed seroconversion**
  - HIV-1 infection as measured by seroconversion (according to the algorithm in Appendix III) during the approximate 4 weeks of follow-up off study product between the PUEV and termination visit.

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Safety and Effectiveness Trial of a Vaginal Matrix Ring with Dapivirine for the Prevention of HIV-1 Infection in Women
Protocol Number:	MTN-020
Short Title:	A Study to Prevent Infection with a Ring for Extended Use (ASPIRE)
Date:	September 28, 2011

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) 6700 B Rockledge Drive Bethesda, MD 20892 USA US National Institute of Mental Health (NIMH) 6001 Executive Boulevard Rockville, MD 20852 USA
IND Sponsor:	International Partnership for Microbicides (IPM) 8401 Colesville Rd., Suite 200 Silver Spring, MD 20910 USA
Monitor:	PPD, Inc. 929 North Front Street Wilmington, NC 28401 USA

1.3 Medical Officer

Medical Officer:	Lydia E. Soto-Torres, MD, MPH 6700 B Rockledge Drive Bethesda, MD 20892-7628 USA

1.4 Clinical Laboratories

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Pharmacology:	MTN NL Pharmacology CORE 600 N. Wolfe Street, Osler 527 Johns Hopkins University Baltimore, MD 21287 USA

1.5 Data Center

Data Center:	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

1.6 Study Operations

Study Operations:	FHI 360 PO Box 13950 Research Triangle Park, NC 27709 USA

2 INTRODUCTION

2.1 Microbicides and Human Immunodeficiency Virus (HIV) Prevention

In 2009, 1.8 million people became newly infected with HIV and 2 million lost their lives to acquired immunodeficiency syndrome (AIDS). According to the Joint United Nations Programme on Human Immunodeficiency Virus-1(HIV)/AIDS (UNAIDS) Global Report, an estimated total number of individuals living with HIV is 33.3 million, of those, 22.5 million reside in sub-Saharan Africa.[1] The on-going development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.

Epidemiologic data published in the UNAIDS/World Health Organization (WHO) "AIDS Epidemic Report 2009" show that 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.[1] Unprotected heterosexual intercourse is currently the leading mode of HIV transmission among women. Correct and consistent use of latex condoms is one proven method of preventing HIV transmission; however, condoms are widely regarded as inadequate prevention options for women, because many women are unable to negotiate condom use with their partners. Most current HIV prevention methods require the consent of the male partner.[2]

Developing HIV prevention options that women can use remains a global concern, given the high rates of HIV infection among women. Vaginal microbicides, which are self-initiated, offer women a critically needed new tool to prevent HIV, complementing existing HIV prevention strategies or future ones that are being developed. An "early generation" of microbicide candidates were tested in Phase 2 trials. The candidates were primarily made of large molecules without direct activity against HIV; none of these products proved effective in preventing HIV transmission. In addition, the ALVAC-AIDSVAX HIV vaccine trial showed only modest effectiveness and research continues to find new vaccine candidates to advance into Phase 3 trials.[3]

Following unsuccessful efforts to develop these non-specific microbicides, the new microbicide candidates, based on highly-specific antiretroviral (ARV) drugs, are currently undergoing extensive safety and effectiveness trials. Unlike early-generation products, which were primarily evaluated in gel formulation delivered via a single-use vaginal applicator used prior to sexual intercourse, ARV-based compounds specifically target HIV infection and can be designed in formulations for more flexible use, including daily or monthly use, independent of sexual activity.

Some recently completed and on-going studies are exploring whether oral daily ARVs taken as pre-exposure prophylaxis (PrEP) are safe and effective for HIV prevention. Recently completed studies are presented below.

CAPRISA 004

In July 2010, in an important milestone for HIV prevention, the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 Phase 2B microbicide trial found a 39% lower HIV infection rate in women using 1% tenofovir gel as compared to the women using a placebo gel when used in a coitally dependant regimen. The drug was found to be 54% effective amongst women who were the highest adherers (gel adherence > 80%). Tenofovir gel is the first ARV-based microbicide to be tested in an effectiveness trial. In addition, tenofovir gel was shown to be safe when used up to 12 hours before sex and again within 12 hours after sex, for a maximum of two doses in 24 hours. Participants who adhered to the dosing regimen in more than 80% of sex acts were the least likely to acquire HIV (54% lower risk of infection).[4]

CDC 4323

CDC 4323 was a Phase 2 extended safety study of tenofovir-disoproxil fumarate (TDF) among HIV-negative men carried out at three US sites. This trial was designed to examine the safety of TDF for HIV prevention in HIV-negative men who have sex with men. Preliminary data announced in July 2010 showed no serious safety concerns on the basis of the preliminary analysis.[5]

iPrEx Study

The iPrEx study, a randomized, double-blind, Phase 3 clinical trial conducted in the United States, Brazil, Ecuador, Peru, South Africa and Thailand was designed to determine whether FTC/TDF (200 mg/300 mg) tablets could safely and effectively prevent HIV infection among men who have sex with men (MSM) and transgendered women who have sex with men, when taken daily.[6] Participants were randomized to receive either oral FTC/TDF or placebo. All participants were routinely counseled about safe sex practices, provided condoms and treated for sexually transmitted infections. Study participants were followed for 3324 person-years (median, 1.2 years; maximum, 2.8 years). Participants who took the daily dose of oral FTC/TDF experienced an average of 44% fewer HIV infections than those who received a placebo pill (95% CI, 15 to 63; P=0.005). A total of 100 participants seroconverted while enrolled in the iPrEx study. Of those, 36 HIV infections occurred among the 1,251 participants randomized to receive FTC/TDF compared with 64 HIV infections among the 1,248 participants who were randomized to receive placebo. Oral FTC/TDF was found to be most effective among participants who were adherent to the daily drug regimen. Participants who took the drug on 50% or more days as measured by pill count, self-report, and dispensation records, experienced 50.2% fewer HIV infections (95% CI, 18 to 70; P=0.006). Those who took the drug on 90% or more days presented 73% fewer HIV infections (95% CI, 41 to 88; P=0.001). Overall, efficacy was greatest among participants who, at the time of enrollment, were at highest risk for HIV acquisition (58%), as captured by self-reports of unprotected receptive anal intercourse. Drug resistance mutations to FTC occurred in 3 participants, 2 of these from the FTC/TDF arm and one from the placebo arm, and all 3 of whom were infected at the time of enrollment. No resistance was observed in any participant with incident HIV infection.

FEM-PrEP Study

The FEM-PrEP Study is a Phase 3, randomized, placebo-controlled, trial of the effectiveness of daily oral FTC/TDF for HIV prevention among HIV-uninfected women in Kenya, South Africa and Tanzania. The FEM-PrEP study enrolled HIV-negative women between the ages of 18 and 35 who were at higher risk for HIV. Higher risk was defined as: 1) has had at least one vaginal sex act in the last two weeks, or 2) has had more than one sexual partner in the last month. Only women who used study-approved contraception at enrollment were eligible for participation. The study was conducted at four sites in three countries (Bondo, Kenya; Bloemfontein and Pretoria, South Africa; and Arusha, Tanzania). All participants in the study were provided comprehensive HIV prevention services, including male and female condoms, intensive risk-reduction behavioral counseling, and testing and treatment for sexually transmitted infections. This trial was designed to close at 72 HIV endpoints; however, during a scheduled review by the trial's Independent Data Monitoring Committee (IDMC) on April 7, 2011, the trial had accumulated 56 endpoints, with 28 endpoints in the FTC/TDF arm and 28 endpoints in the placebo arm, leaving 16 endpoints until the trial was complete.[7] The trial was stopped early due to futility. No significant safety concerns were noted. Pregnancy rates were noted to be higher in women taking hormonal contraceptives (at the onset of participation) and FTC/TDF compared with those taking hormonal contraceptives and the placebo. Final study results are expected to be available in late 2011 or early 2012.

TDF2

The TDF2 Study is a Phase 2B study that assessed the safety, adherence and efficacy of daily oral FTC/TDF in 1,200 HIV-uninfected heterosexual male and female participants aged 18-39.[8] The trial, originally known as the Botswana PrEP Study, began in 2005 as a Phase 3 trial of TDF. In 2007, the study product was changed to FTC/TDF. In 2009, the completed enrollment of 1,200 participants, but due to lower than expected HIV incidence and suboptimal retention, it was determined that the study would not be able to answer its primary objective of efficacy. The trial continued, but with intent to evaluate safety and adherence. Of the 1,200 participants in the TDF2 Study, 45% of whom were women, 601 were randomly assigned to FTC/TDF, and 599 were assigned to placebo. All participants were provided comprehensive HIV prevention services, including male and female condoms, intensive risk-reduction behavioral counseling, and testing and treatment for sexually transmitted infections. During the study, 33 of 1,200 participants acquired HIV (nine of the 601 participants on the FTC/TDF arm and 24 participants of the 599 on the placebo arm), corresponding to a 62.6% reduction in HIV acquisition for those assigned to FTC/TDF, compared to placebo (HR 0.37, CI 21.5-83.4, P = 0.013). Among 21 total HIV endpoints in women in the trial, 7 were in the FTC/TDF arm and 14 were in the placebo arm. While results for the subset of women in the trial did not meet statistical significance (HR 0.51, CI -0.217-80.8, P = 0.107), a non-intent-to-treat (ITT) analysis among women thought to have a supply of study drug (3 HIV endpoints in the FTC/TDF arm and 13 in the placebo arm) found an estimated efficacy of 75.5%, P = 0.021. No significant safety concerns were noted, though participants randomized to the FTC/TDF arm did experience more nausea, vomiting, and dizziness than those randomized to placebo.

In addition, tenofovir gel is also being tested in a non-coitally dependant regimen of once-daily product in the MTN-003 (VOICE). VOICE is a Phase 2B trial currently on-going in Uganda, Zimbabwe, and South Africa. An additional confirmatory Phase 3 trial, Follow on Africa Consortium for Tenofovir Studies (FACTS) 001, with tenofovir gel plans to use the same coitally dependant regimen of CAPRISA 004 and is planned to start in 2011.

With successful proof-of-concept that an ARV-based microbicide can reduce the risk of HIV-1 acquisition, ARV prevention approaches have the potential to transform the response to the HIV/AIDS epidemic. In addition to confirmatory work on tenofovir gel, further trials are needed on microbicides that contain different ARV compounds in different formulations using different dosing strategies, to provide options and improve upon the level of effectiveness seen in CAPRISA 004.

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. As seen in the CAPRISA 004 trial higher adherence to product may translate into higher effectiveness of the product. It is likely that products that can be applied less frequently will be more acceptable and will achieve better adherence. Vaginal rings that need to be replaced every 4 weeks may have benefits over dosage forms that need to be used more frequently. The dapivirine (25 mg) silicone elastomer vaginal ring (VR) is the lead VR candidate for advancement to Phase 3 clinical testing.

Multiple clinical trials[9-15] 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.

2.2 Dapivirine Vaginal Ring

2.2.1 Description

Dapivirine, a non-nucleoside reverse-transcriptase inhibitors (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.[14] The dapivirine matrix VR is a flexible ring containing 25 mg of drug substance dispersed in a platinum-catalyzed-cured silicone matrix. Dapivirine is known to be well-suited for delivery via VR, as evidenced by favorable safety and pharmacokinetic data to date described below.

Dapivirine was originally developed by Tibotec Pharmaceuticals (Titusville, NJ) as an oral ARV compound and was tested in Phase 1 and 2 clinical trials in more than 200 participants.[12] Although first conceived as an oral therapeutic, dapivirine became a promising topical microbicide candidate due to its proven *in vitro* and *in vivo* efficacy

and favorable safety profile as well as its physical and chemical properties. Dapivirine has potent activity against wild-type HIV-1 strains and strains harboring different resistance-inducing mutations. Dapivirine's ARV profile is superior to that of other NNRTI drugs, including nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). Comparable to other NNRTIs, *in vitro* tests have also shown that dapivirine has limited efficacy against HIV-2 and no efficacy against common sexually transmitted infections (STI). Dapivirine is therefore not intended to have activity against HIV-2 or other STIs, nor does it have any contraceptive properties.[16] Detailed information on dapivirine is available in the Dapivirine VR Investigator's Brochure (IB).[17]

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

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

The safety and tolerability of dapivirine has been evaluated by IPM and Tibotec Pharmaceuticals in both animal and human studies via the oral and vaginal routes. Below is a summary of the data collected through these studies.

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 will contain 25 mg of dapivirine. This is the same drug load as was used in dapivirine rings previously tested and/or planned for in five trials involving 77 participants, including two 28-day trials (IPM) involving HIV-uninfected women using Ring-004. The current formulation is a dapivirine matrix VR containing 25 mg of drug substance dispersed in a platinum-catalyzed-cured silicone matrix. In addition, platinum-catalyzed matrix VRs containing 25 mg of dapivirine were studied in IPM 013

over an approximately 8-week period with a 4-week follow-up among healthy, sexually active HIV-uninfected women. Finally, IPM 015 a Phase 1/2 double-blind placebo-controlled trial randomized 140 women to dapivirine VR use. Participants from Kenya, Malawi, South Africa, and Tanzania inserted a dapivirine VR once every 28 days over a 12-week period. Data analysis of this trial is ongoing.

2.3 Placebo VR

2.3.1 Description

The placebo VR is a flexible, platinum-catalyzed-cured silicone matrix ring which contains no active drug.

2.3.2 Mechanism of Action

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

2.3.3 Strength of Study Product

The placebo VR contains no active drug.

2.4 *In vitro* Studies

2.4.1 *In vitro* Studies of Dapivirine

Anti-HIV-1 Activity

The activity of dapivirine against wild-type (wt) HIV-1, African isolates of HIV-1 (including subtype C virus), and a panel of NNRTI-resistant viruses has been established using *in vitro* models, with 50% effective concentration (EC_{50}) values ranging from 0.3 ng/mL (0.9 nM) against laboratory isolates to <33 ng/mL (<100 nM) for HIV-1 isolates encoding one or more known NNRTI resistance mutations.[14,18]

Resistance

HIV-1 virus breakthrough in the presence of dapivirine was initially evaluated in studies in which cells were infected with wild-type HIV-1 laboratory strains at high multiplicity of infection and in the presence of high concentrations of dapivirine. At 40 nM virus breakthrough occurred between 4 and 7 days, at 200 nM between 7 and 10 days and at 1 µM it took up to 30 days to observe virus growth. In all cases mutations were present. Virus selected with the Y181C mutation was resistant to dapivirine. Subsequently, cells were infected with wild-type HIV-1 at low multiplicity of infection and were exposed to very low concentrations of dapivirine to mimic the extremely low systemic concentrations observed in the first clinical trial of one formulation of topical dapivirine (Gel-001).

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

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

The significance of Y181C in a single clone at 0.01 nM in the 31-day culture is not clear. It is possible that the sensitive single genome sequencing technology detected some of the pre-existing natural variants present in a virus population in the absence of selective pressure. It was concluded that prolonged exposure to low concentrations of dapivirine can result in selection of viruses carrying NNRTI resistance-associated mutations, but the clinical relevance of these *in vitro* data is not known.[14]

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.[14]

2.5 Condom Compatibility Studies of Dapivirine

Condom compatibility studies have not been conducted with the VR; however, chemical compatibility studies with different dapivirine containing gel formulations were conducted on the following types of condoms:[19]

- 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 airburst and tensile condom properties tested pre- and post-treatment.

All types of condoms met the acceptance criteria established in the protocol for the mean values of the treated samples after treatment with gels. Additionally, all airburst data for treated samples met the ISO 4074:2002 and ASTM D3492 release criteria requirements.

2.5.1 Nonclinical Studies of Dapivirine

Pharmacokinetics

Systemic exposure to dapivirine was low following vaginal administration of dapivirine gels to rabbits.[14] Much higher systemic exposures were obtained in single-dose oral and subcutaneous toxicity studies in mice and rats, and in repeat dose oral toxicity studies in rats, dogs and monkeys. The free fraction of dapivirine in plasma was 0.19-0.34% in the male rat, 0.18-0.39% in the female rat, 0.21-0.22% in the dog and 0.15% in humans. In rats, tissue-to-plasma area under plasma concentration-time curve $(AUC)_{0-24}$ ratios following a single oral dose were 11 in liver, 7-8 in lung, kidney and adrenals, about 4 in spleen and lymph nodes, and 2-3 in brain, heart and muscle. Plasma/tissue equilibrium was rapid, and there was no undue retention of dapivirine in tissues. Following a single oral or vaginal dose of ^{14}C-dapivirine, absorption and distribution of drug-related material to the tissues was moderate in non-pregnant and slow in pregnant female rats. Vaginal dosing did not result in greater distribution to the reproductive tissues (except the vaginal wall) than oral dosing. For virtually all tissues, maximal concentrations after vaginal dosing were <1% of those after oral dosing. Drug-related material was shown to freely cross the placenta to the fetus. In dogs, dapivirine concentrations following oral administration for 14 days were about 9 times higher in liver and muscle, and about 5 times higher in lymph nodes and brain than in plasma. Preliminary metabolism studies demonstrated the presence of free and conjugated metabolites in rats, dogs, monkeys and humans, but the molecular structures have not been elucidated. There was evidence of extensive cytochrome P450 (particularly CYP3A4) mediated metabolism.[14]

Toxicology

The toxicity of dapivirine has been evaluated in a comprehensive program of preclinical studies. These are described in the IB and included repeat dose vaginal toxicity studies in rabbits using gel formulations of dapivirine at concentrations up to 20 mg/mL for 14 days, up to 5 mg/mL for 13 weeks or up to 2 mg/mL for 39 weeks (dose volume = 1 mL/day).[17] No local or systemic toxicity was identified in any of these studies. In addition, studies of up to 26 weeks duration were completed in rats and dogs via the oral route. The no-observed-adverse-effect-level (NOAEL) in both species following oral administration was 20 mg/kg/day. C_{max} at the NOAEL was 0.39 µg/mL in rats and 1.21 µg/mL in dogs, which was more than 1000 and 3400 times, respectively, the maximum mean plasma concentration (0.355 ng/mL) in women using a dapivirine ring

(Ring-004) for 28 days. AUC at the NOAEL was 4.80 µg.h/mL in rats and 12.98 µg.h/mL in dogs, which is over 1500 and 4200 times, respectively, the mean AUC (3.022 ng.h/mL) in women using Ring-004 for 28 days.

Mutagenesis

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

Reproductive Toxicity

In rats, some effects on the developing fetus were observed following oral administration at maternally toxic doses (80 and 320 mg/kg) of dapivirine. However, there were no effects in rats at the maternally non-toxic dose of 20 mg/kg/day, or in rabbits at up to 90 mg/kg. No toxicity to maternal animals or the developing embryo/fetus was seen following vaginal dosing in embryo-fetal development studies in rats (up to 3.3 mg/mL using a dose volume of 0.2 mL/kg) and rabbits (up to 2 mg/mL using a dose volume of 1.0 mL).[17]

Vaginal reproductive toxicity trials in rats and rabbits using a formulation of dapivirine gel (Gel-001) at nominal concentrations up to 3.3 mg/mL (10 mM) or another formulation of dapivirine gel (Gel-002) at up to 2.0 mg/mL (0.2%) did not identify any adverse effects on the maternal animals or the developing embryo/fetus.[17]

Effectiveness

Dapivirine blocked vaginal transmission of HIV-1 in a hu-SCID mouse model in which animals received a single vaginal application of dapivirine gel (candidate research gels containing either Carbopol 940 or hydroxyethylcellulose (HEC)) prior to a non-invasive vaginal challenge with human peripheral blood lymphocytes (hu-PBL) previously infected *in vitro* with CCR5-tropic and dual tropic (CCR5/CXCR4) HIV-1 strains. Dapivirine prevented a systemic infection with either CCR5 or CCR5/CXCR4 virus strains at concentrations of 2.25 µM (0.7 µg/mL) and higher. The efficacy rate ranged from approximately 70 to 100%, depending on the vaginal gel formulation. The protection resulted directly from the ARV activity of dapivirine, since placebo gels failed to protect and since dapivirine did not show toxicity using mock-infected hu-PBL. Results were better with gels of lower viscosity, probably reflecting the ease with which the vaginal gel was applied to the vagina and thus either the uniformity of distribution over the entire vagina/cervix or the non-traumatic application of the vaginal gel.[18]

Anti-HIV Activity

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.[14,18] 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 (IC50= 0.1 nM [0.03 ng/mL]).[17]

2.6 Clinical Studies

2.6.1 Clinical Studies of Dapivirine

To date, 25 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted or are currently underway: six trials of dapivirine VRs in which 222 participants were assigned to dapivirine VRs, eight trials of dapivirine vaginal gel in which 491 participants used dapivirine vaginal gel, and 11 trials of oral dapivirine among 211 participants.[14]

Pharmacokinetics

Dapivirine vaginal rings

Previously, IPM conducted a 28-day trial (IPM 018) in HIV-uninfected women using tin catalyzed silicone matrix and reservoir rings containing 25 mg of dapivirine. The goal of that trial was to determine the safety and PK of dapivirine delivered from these rings. The rings were found to be generally safe and well-tolerated with a promising drug release profile.[20]

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. 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, well below plasma levels at the maximum tolerated dose (MTD) 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.[18]

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

IPM 013 was a Phase 1, randomized, double-blind, placebo-controlled trial conducted over three months in 48 healthy, HIV-negative, sexually active women, 18 to 40 years of age in Belgium. This trial evaluated the delivery of dapivirine from a matrix (platinum-catalyzed) ring 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. 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. Plasma concentrations did not exceed 553 pg/mL, while the highest vaginal fluid concentration obtained was 171 µg/g. Data suggest that dapivirine is readily released from the ring and absorbed into the surrounding tissue and into the bloodstream in concentrations. Concentrations of dapivirine collected within 4 hours of ring insertion show quantifiable plasma (LLOQ = 3.00 pg/mL) and vaginal fluid (LLOQ = 0.4 ng) after insertion of the first ring.

Other Vaginal Dapivirine Formulations

Dapivirine Gels 4759 and 4789

Gels 4759 and 4789 are being tested in IPM 020 and IPM 014A.[14] IPM 020 is a double-blind, randomized, placebo-controlled Phase 1/2 expanded safety study involving approximately 180 healthy, sexually active HIV-uninfected women to assess the safety of Dapivirine Gel 4759, 0.05% 2.5g and Dapivirine Gel 4789, 0.05% 2.5g as compared to the HEC-based Universal Placebo gel. As of June 2011, data for this study was currently under analysis. IPM 014A is a double-blind, randomized, placebo-controlled Phase 1/2 Study to Evaluate the Safety and Acceptability of Dapivirine Gel 4759, 0.05%, 2.5g, conducted using daily monitored adherence in 320 healthy, HIV-uninfected women to determine whether the gel is safe for daily use by women in Kenya, Malawi, Rwanda, South Africa and Tanzania. As of June 2011, this study was currently ongoing.

Dapivirine Gel 4750

Gel 4750 was studied in IPM 012. Gel 4750 included excipient Vitamin E TPGS (dispersing agent, 0.50%); otherwise the gel formulations (Gel 4750 and Gel 4759) were essentially the same.[14] In IPM 012, the safety and pharmacokinetics of two formulations of dapivirine vaginal gel were compared with the HEC-based Universal Placebo gel in 36 healthy, HIV-uninfected, sexually abstinent women 18 to 40 years of age. This Phase 1, randomized, double-blind, placebo-controlled trial was conducted at one research center in Belgium. Women were randomized in a 1:1:1 ratio to once daily (QD) applications of Gel 4750 (0.05%, 2.5 g), Gel 4789 (0.05%, 2.5 g), or placebo gel

for 11 days (Day 1 followed by a 3-day washout period and then for 10 consecutive days, Days 5-14). Dapivirine concentrations were measured in cervicovaginal fluids and plasma on Days 1, 2, 5, 9, 11, 14-17, 19, 21, and 24.

Systemic absorption of dapivirine was low. C_{max} and $AUC_{0\text{-}24h}$ values for dapivirine in plasma were slightly higher for Gel 4750 than Gel 4789 on Days 1 and 14; however, the differences did not achieve statistical significance. For both gels, Day 14 values were 2- to 4-fold higher than values on Day 1. T_{max} was variable; on Day 1 the mean was 23.5 hours for both gels, whereas by Day 14 means were 10-12 hours. Terminal half-life was much longer in plasma (73-90 hours) than in cervicovaginal fluids (15-17 hours).[21]

Safety

Clinical Trials of Dapivirine Vaginal Rings

Table 1: Clinical Phase I/II 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	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
TOTAL 393 participants:			12	18	8	184	183

* Tin-catalysed matrix ring.
** Platinum-catalysed matrix ring.
# Data analysis ongoing; results pending.

Across all clinical trials with multiple ring configurations in healthy participants, the dapivirine VR was generally safe and well tolerated.[18] No serious adverse events (SAEs) were reported in participants using the VR. One participant using the placebo ring experienced two SAEs, bacterial gastroenteritis and pyrexia, which were assessed by the investigator as unrelated to the investigational product. No participants were discontinued from the VR due to investigational product-related adverse events (AEs). The first dapivirine VR tested in humans, Ring-001, consisted of two reservoir cores of dapivirine surrounded by a controlled-release outer sheath of silicone elastomer. Ring-001 was tested in a Phase 1, open-label, crossover trial in 12 healthy, sexually abstinent, HIV-uninfected women at a single research center in Belgium (IPM 001).[11] Women used the placebo ring for 7 days followed by the dapivirine ring for 7 days. There were no 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, was used in a later clinical trial. Ring-002 was tested in a Phase 1, randomized, placebo-controlled trial conducted at a single research center in Belgium (IPM 008).[11] 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. Twenty-four healthy, HIV-uninfected women 18 to 35 years of age were randomly assigned (1:1:1) to dapivirine matrix ring, dapivirine reservoir ring, or placebo ring for 28 consecutive days. No SAEs were reported during the study. No TEAEs were assessed by the investigator as definitely or probably related to the ring, and similar percentages of participants in the dapivirine and placebo ring groups had TEAEs considered to be possibly related to the ring.

The current formulation, Ring-004, is a dapivirine matrix VR containing 25 mg of drug substance dispersed in a platinum-catalyzed-cured silicone matrix. Ring 004 was tested in a 28-day trial (IPM 024) conducted in Belgium, involving 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 assessed by the investigator were judged to be related to the study agent. Most dapivirine VR group participants, 87.5% (7/8), experienced at least one TEAE. Of the women in the dapivirine VR group who experienced a TEAE, 50% (4/8) reported headache. Two to four women (25% to 50%) with dapivirine VRs experienced Grade 1 or Grade 2 metrorrhagia, vulvovaginal discomfort and nasopharyngitis TEAEs. One participant experienced a Grade 1 vaginal hemorrhage in the dapivirine VR group.[18]

Clinical Trials of Other Vaginal Dapivirine Formulations

Dapivirine Gel 001

Dapivirine gel was tested in a 2-part, Phase 1 trial (TMC120-C127) in 48 HIV-uninfected women and 16 HIV-positive women.[14] Twice-daily application of one of three concentrations of Gel-001 (0.0008%, 0.0016%, or 0.0049%) or a placebo gel was investigated. There were no apparent differences in safety parameters between the three concentrations of Gel-001 and the placebo gel, nor were there apparent safety differences between sexually active and sexually abstinent women. Dapivirine concentrations in plasma remained essentially level in all three dose groups after maximum concentrations were reached 4 to 8 hours after gel application. The vaginal gels were well-tolerated by healthy participants and HIV-positive participants.[15]

Dapivirine Gel 002

To improve solubility and stability, a new vehicle was developed for vaginal delivery of dapivirine.[14] This new gel was tested in three Phase 1/2 trials: IPM 003, IPM 004 and IPM 005B. In IPM 003, conducted in South Africa, Rwanda, and Tanzania, 112 women used one of three concentrations of dapivirine gel or a placebo gel for 42 days.[12] In IPM 004, a pharmacokinetics trial conducted in South Africa, 18 women used one of three concentrations of dapivirine gel for 10 days. In IPM 005B, conducted in Belgium, 36 women used dapivirine gel (0.02%, 2.65 g) or Universal Placebo gel for 42 days. No treatment related SAEs were observed in these studies. In general, dapivirine gel was well-tolerated with no safety concerns or dropouts due to investigational product-related AEs.

Dapivirine Gels 4750 and 4789

The pharmacokinetics of candidates Gel 4750 and Gel 4789 (both 0.05%, 2.5 g) were tested in IPM 012, which was conducted in Belgium in 36 women who applied the vaginal gel QD for 11 days.[14] There were no SAEs or discontinuations due to TEAEs in the trial. Most participants (83-100%) in each group had at least one TEAE during the trial. Headache was the event that occurred most often; 42-67% of participants in the dapivirine gel groups and 42% of participants in the placebo gel group reported at least one headache. For most participants with headaches (13/18; 72%), the event was assessed as possibly related to the investigational product.

All but two TEAEs were assessed as Grade 1 (mild). One subject in the Gel 4789 group had a Grade 2 (moderate) headache assessed as possibly related to the investigational product, and a different subject in the same group had Grade 2 pyrexia assessed as not related to the investigational product. Thirty-four percent (36/105) of TEAEs were assessed as possibly related to the investigational product, and one subject in the Gel 4789 group had two episodes of vulvovaginal pruritus that were assessed as probably related. Among participants using Gel 4750, the other TEAEs deemed related to the gel included malaise (1/12) and cervix erythema (1/12).

IPM 014B examined the safety of once daily application of Gel 4789 (0.05% dapivirine) over a six-week period as compared with a matching vehicle placebo gel in a Phase I/2, randomized, double-blind, placebo-controlled trial in 100 healthy, sexually active, HIV-negative women at three sites in South Africa. Women were randomized 1:1 to once daily vaginal application of Gel 4789 or placebo gel for 42 days. No SAEs or discontinuations due to TEAEs were reported during the trial.

Most participants reported at least one TEAE during the trial, none of which was assessed as definitely related to gel use. Eighteen (36%) of participants in the dapivirine gel group and 13 (26%) of participants in the placebo gel group experienced TEAEs considered to be probably or possibly related to the gel. All TEAEs were assessed as Grade 1 or Grade 2, with the exception of a grand mal convulsion, experienced by a study participant in the placebo arm. This participant had been enrolled in error, having had a history of epilepsy. Metrorrhagia was the AE reported most frequently (11 of 100 study participants; 7 of 50 randomized to placebo gel and 4 of 50 randomized to dapivirine gel). All were reported as mild (Grade 1) intermenstrual or breakthrough menstrual bleeding, and for 62% of the women for whom metrorrhagia was reported, it was thought to be unrelated to study product. Events that occurred in more than one participant and were thought to be possibly or probably related to dapivirine gel included bacterial vaginitis, headache, vaginal candidiasis, urinary tract infection, vulvovaginal mycotic infection, vaginal discharge and vulvovaginal pruiritus. In the placebo gel arm, bacterial vaginitis, headache, vaginal candidiasis, and vulvovaginal mycotic infection were considered to be related to placebo gel.

Two studies of dapivirine gel have results pending, IPM 014A is a study examining the safety and acceptability study of Gel 4759 in 280 HIV-negative women (once daily gel application for 42 days), and IPM 020 is an expanded safety trial of once daily application of two formulations of dapivirine gel (Gel 4759 or Gel 4789) as compared with placebo for 84 days in 128 women.

In addition to the safety acceptability and PK studies noted above, a male tolerance study of dapivirine gel (Gel 4759), MTN-012/IPM 010, is underway with results expected to be available in the fourth quarter of 2011. Forty-eight males (24 circumcised and 24 uncircumcised) were enrolled into this Phase 1 study which will provide valuable information regarding tolerability after 7 days of once-daily penile application of dapivirine gel.

Oral Dapivirine

There have been 11 oral administration trials in which a total of 211 participants have been dosed with dapivirine. The maximum tolerated dose established was 350 mg for a single dose, and for multiple doses, 300 mg twice a day for 14 days. There were no deaths during clinical trials of oral dapivirine, and no trials were stopped for safety reasons. A total of 10 participants stopped dapivirine treatment prior to trial completion for safety reasons, six of whom stopped due to a clear dose dependent increase in central nervous system (CNS) and gastrointestinal TEAEs, thereby establishing the maximum tolerated dose at 300 mg twice a day. These TEAEs resolved within 1-2 days

after discontinuation of use of oral dapivirine. One of the discontinuations was classified as an SAE, with hospitalization due to elevated liver function tests. This participant was also infected with hepatitis C virus. The only other SAE noted in these trials was a hospitalization due to a bicycle accident.

Pregnancy Outcomes
There are no adequate and well-controlled studies of dapivirine in pregnant women.

In conclusion, these reassuring safety data and promising anti-HIV-1 activity data from 25 Phase 1 and Phase 1/2 clinical trials make dapivirine an ideal candidate for a Phase 3 safety and effectiveness clinical trial.[14]

2.6.2 Clinical Studies of Placebo VR

Similar placebo VRs were studied in IPM 024.

2.7 Study Hypothesis and Rationale for Study Design

2.7.1 Study Hypothesis

Safety Profile
The protocol team hypothesizes that the active study product will be safe, well-tolerated and acceptable for extended use among healthy sexually-active women.

Effectiveness
The null hypothesis is that the active product will be no more than 25% effective. The trial is powered to detect at least 60% effectiveness in preventing acquisition of HIV-1 relative to placebo, and to rule out effectiveness of 25% or lower.

2.7.2 Rationale for Study Design

Based on *in vitro*, *in vivo*, and *ex vivo* studies described in the Dapivirine VR IB, dapivirine shows great promise as a topical microbicide to prevent HIV-1 infection.[17]

Vaginal rings have already been developed and approved as delivery methods for medications. For example, NuvaRing® a contraceptive VR made of the copolymer evatane, in which 2.7 mg of ethinyl estradiol (EE) and 11.7 mg of etonogestrel (ENG) are equally dispersed, has been found to be both effective and acceptable.[22] In an acceptability study involving 1,950 NuvaRing® users, 45.5% of women cited their reason for liking the VR was “not having to remember anything.[23] These contraceptive ring data are encouraging as microbicide ring effectiveness correlates with consistent and correct use. It is likely that products that can be applied less frequently will be more acceptable to users, achieve better user-adherence, and may lead to increased effectiveness. Vaginal rings that need only be replaced every 28 days may have benefits over dosage forms that need to be used more frequently as well as offer a wider choice of microbicide formulations for women if proven effective.

Pfizer (formerly Pharmacia and Upjohn Company) has marketed Estring® (estradiol vaginal ring), a VR that is also made from silicone elastomer and contains estradiol used to treat local symptoms of urogenital atrophy, since 1993. Prior to the launch of Estring®, the biological safety of the silicone elastomer was studied in various *in vitro* and *in vivo* test models. The results show that the silicone elastomer is non-toxic, non-pyrogenic, non-irritating, and non-sensitizing.[24]

Femring® (estradiol acetate vaginal ring), a hormone replacement product approved in June 2003 by the United States (U.S.) Food and Drug Administration (FDA) treats menopause-induced vasomotor symptoms (e.g., hot flushes) and symptoms of vulvar and vaginal atrophy (e.g., dryness).[25] Although these rings are not exactly the same as the IPM ring, the extensive clinical trial and post-marketing experience gained from these products provides further assurance of the safety of silicone elastomer rings as vaginal drug delivery devices. An acceptability trial of the silicone elastomer ring used in Femring® (but containing no drug) among postmenopausal women in the U.S. demonstrated very high acceptability and ease of use.[26] IPM recently evaluated the acceptability and safety of a similar placebo VR in the IPM 011 study (n=170).[25] This study confirmed that the placebo ring was safe and acceptable to users and their male partners.

MTN-020, A Study to Prevent Infection with a Ring for Extended Use (ASPIRE) has been developed to compare the safety and effectiveness of dapivirine (25 mg) in a silicone elastomer vaginal matrix ring (Ring-004) with a placebo VR when inserted once every 28 days for the prevention of HIV-1 infection in healthy, HIV-uninfected sexually active women.

2.7.3 Incorporating Emergent Effective HIV-1 Prevention Strategies

As candidate microbicides continue to demonstrate evidence of efficacy, the potential for one or more licensed HIV-1 prevention strategies may soon become a reality. The ASPIRE Protocol Team acknowledges that an effective agent may require changes to the current protocol design. The team plans to follow all relevant national policies regarding HIV-1 prevention and will actively consult with stakeholders in the event an effective intervention is approved. 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 Work Group (CWG).

3 OBJECTIVES

3.1 Primary Objectives

- To determine the *effectiveness* of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks, in preventing HIV-1 infection among healthy sexually active HIV-uninfected women

- To assess the *safety* of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks over the investigational product use period

3.2 Secondary Objectives

- To evaluate the *acceptability* of the study VR (dapivirine or placebo) in HIV-uninfected women, when inserted once every 4 weeks over the investigational product use period.

- To evaluate the *adherence* to the study VR (dapivirine or placebo) in HIV-uninfected women, when inserted once every 4 weeks over the investigational product use period.

- To assess the frequency of HIV-1 *drug resistance* in women who acquire HIV-1 infection while using the investigational product

- To evaluate the *relationship between drug concentration* and *HIV-1 seroconversion.*

3.3 Exploratory Objectives

- Describe changes in the *genital microenvironment*

- To assess *correlation of steady-state drug concentration and adherence measures*

- To assess the *incidence of HIV-1 seroconversion* during 4 weeks off study product, between the PUEV and termination visit.

4 STUDY DESIGN

4.1 Identification of Study Design

ASPIRE is a multi-site, double-blind, randomized, placebo-controlled Phase 3 trial to evaluate the safety and effectiveness of dapivirine (25 mg) in a silicone elastomer

vaginal matrix ring, inserted once every 4 weeks for the prevention of HIV-1 infection in healthy, sexually active HIV-uninfected women, when compared to a placebo VR.

4.2 Summary of Major Endpoints

- **Effectiveness**
  - HIV-1 infection as measured by seroconversion at the end of the investigational product use period with seroconversion defined by the algorithm in Appendix III
- **Safety**
  - Grade 2 AEs, judged to be related to study product
  - Grade 3 and 4 AEs
  - All serious adverse events

4.3 Description of Study Population

Approximately 3476 sexually active HIV-uninfected women 18-45 years of age who meet eligibility criteria as described in Sections 5.2 and 5.3 will be enrolled and randomized in a 1:1 ratio to receive either a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine or a placebo VR.

4.4 Time to Complete Accrual

Accrual is expected to be completed in approximately 12 months.

4.5 Study Groups

Two study groups are planned. The two study groups are as follows:

1) Dapivirine VR group
2) Placebo VR group

4.6 Expected Duration of Participation

Each participant will engage in the screening process for up to 4 weeks (28 days) prior to enrollment and will use the product until 120 events (HIV-1 seroconversions) are observed in the trial. Based on the anticipated rate of accrual of participants and projected HIV-1 incidence in the trial, it is expected that 120 events will be reached approximately 12 months after the last participant enrolls, and thus all participants are anticipated to have a minimum of 12 months on study product. Each participant will complete approximately 4 additional weeks of follow-up off study product to assess for potential delayed seroconversions due to masked infections that are not detected during the product use period.

4.7 Sites

Sites selected by the MTN Executive Committee will participate in ASPIRE.

5 STUDY POPULATION

5.1 Selection of the Study Population

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

5.1.1 Recruitment

Participants are recruited from a variety of sources across sites, including sexually transmitted disease (STD) clinics, family planning clinics, and post-natal clinics, as well as community-based locations. In addition, participants may be referred to the study from other local research projects and other health and social service providers serving the target study population. Recruitment materials are approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use. Advice regarding these materials will be sought from site community representatives before they are submitted to the IRB/EC for review.

5.1.2 Retention

Once a participant is enrolled/randomized in ASPIRE, the study site makes every effort to retain her in follow-up to minimize possible bias associated with loss-to-follow-up. Standard operating procedures (SOPs) for participant retention to target loss-to-follow-up rates that do not exceed the incidence rate of the primary study endpoint are required of each site. As such, an average annual retention rate of 95% is targeted across sites. All study sites are responsible for developing and implementing local SOPs to achieve this. Components of such procedures may include the following:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process, and re-emphasis at each study visit. Also as part of the informed consent process, encouragement of participants to discuss potential study participation with their husbands/partners and other influential family members.
- Thorough explanation of the importance of both study groups to the overall success of the study.
- Collection of detailed locator information at the study screening visits, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.

- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow-up on missed visits, including the allowance of off-site visits.
- Mobilization of trained outreach workers to complete in-person contact with participants at their homes and/or other locations.
- Regular communication with the study community at large to increase awareness of HIV/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits.

Study sites may use a participant tracking database to facilitate visit scheduling and timely identification and follow-up on missed visits. The MTN Statistical Data Management Center (SDMC) generates monthly reports on the number and percentage of participants completing follow-up visits throughout the course of the study. The protocol team, as well as the MTN Study Monitoring Committee (SMC), track retention rates closely and work with study sites as needed to take any required action to address below-target retention rates.

5.2 Inclusion Criteria

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

1) Age 18 through 45 years (inclusive) at screening, verified per site SOPs; within this range, sites may restrict the upper age limit per site SOPs, to target women at high risk of HIV infection

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) Per participant report, sexually active, defined as having vaginal intercourse at least once in the 3 months prior to screening

6) 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 device (IUD); and sterilization (of participant, as defined in site SOPs)

7) 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

   Note: Tampons may be used for the duration of the trial.

5.3 Exclusion Criteria

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

1) Per participant report at screening:
   a) Intends to become pregnant during study participation
   b) Plans to relocate away from the study site during study participation
   c) Plans to travel away from the study site for more than 8 consecutive weeks during study participation

2) Is pregnant

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

3) Currently breastfeeding

4) Diagnosed with urinary tract infection (UTI)

   Note: Otherwise eligible participants diagnosed with UTI during screening are offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 28 days of obtaining informed consent for screening, the participant may be enrolled.

5) Diagnosed with pelvic inflammatory disease, an STI or reproductive tract infection (RTI) requiring treatment per current WHO guidelines

   Note: Otherwise eligible participants diagnosed during screening with pelvic inflammatory disease or STI/RTI requiring treatment per WHO guidelines — other than asymptomatic BV and asymptomatic candidiasis — are offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 28 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.

6) Has a clinically apparent Grade 2 or higher 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: Cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the Investigator of Record (IoR)/designee is considered expected non-menstrual bleeding and is not exclusionary.

Note: Otherwise eligible participants with exclusionary pelvic exam findings may be enrolled/randomized after the findings have improved to a non-exclusionary severity grading or resolved. If improvement to a non-exclusionary grade or resolution is documented within 28 days of providing informed consent for screening, the participant may be enrolled.

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

   a) Known adverse reaction to any of the study products (ever)
   b) Known adverse reaction to latex (ever)
   c) Chronic vaginal candidiasis
   d) Non-therapeutic injection drug use in the 12 months prior to Screening
   e) Post-exposure prophylaxis (PEP) for HIV exposure within 6 months prior to enrollment
   f) Last pregnancy outcome 90 days or less prior to enrollment
   g) Gynecologic or genital procedure (e.g., tubal ligation, dilation and curettage, piercing) 90 days or less prior to enrollment
   h) Recent participation in any other research study involving drugs, medical devices, vaginal products, or vaccines, within 60 days of enrollment
   i) Participation in the MTN-003, Vaginal and Oral Interventions to Control the Epidemic (VOICE) clinical trial, or any other HIV prevention study using systemic or topical antiretroviral medications, within 12 months of enrollment
   j) As determined by the IoR/designee, any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, including active tuberculosis

8) Has any of the following laboratory abnormalities at Screening Visit:
   a) Aspartate aminotransferase (AST) or alanine transaminase (ALT) Grade 1 or higher 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)
   b) Creatinine Grade 2 or higher 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)
   c) Hemoglobin Grade 2 or higher 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)
   d) Platelet count Grade 1 or higher 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)
   e) Pap result Grade 2 or higher 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. Women with a Grade 1 abnormal Pap smear can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology). Need for a repeat Pap within 6 months does not preclude enrollment prior to that result becoming available.

9) Has any 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 Co-enrollment Guidelines

As indicated in Section 5.2, 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 coenroll in the following types of studies at the discretion of the IoR/designee:

- Participants may take part in ancillary studies approved by MTN-020 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 MTN-020 Protocol Chair

Should any participant report or should study staff discover concurrent participation in contraindicated studies after enrolling in MTN-020, 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

Each participant will be randomized to one of two study regimens:

Table 2: Study Regimen

Group	N	Group Description
A	1738	Dapivirine VR, containing 25 mg dapivirine
B	1738	Placebo VR

Each participant will receive a VR containing either 25 mg dapivirine or a placebo VR in a 1:1 ratio. The VR should be worn for approximately 28 consecutive days at a time but not more than 35 days before being replaced. A new VR will be inserted into the vagina at the Enrollment Visit and at each subsequent monthly visit. The previously inserted ring will be removed by the participant or clinician/designee at each monthly visit. The participant will be followed for approximately 4 weeks following the final VR removal.

6.2 Administration

The participant will self-insert (or by clinician, if necessary), the study VR at the Enrollment Visit and each subsequent visit when a VR is dispensed. In the rare event that a participant is unable to attend their next scheduled visit, IoRs may use their discretion to dispense a maximum of one additional ring. In this situation, the participant will insert the ring at home.

Study participants will be given detailed instructions in the clinic on proper VR insertion and removal procedures at the Enrollment Visit and as needed at subsequent visits. Hands should be thoroughly washed before and after study VR insertion and/or removal. The attempt of these procedures should be documented at Enrollment. Additional details on administration (ring insertion, removal, procedures in the event of expulsion or loss) will be provided in the ASPIRE Study Specific Procedures (SSP) Manual.

6.3 Study Product Formulation

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

6.3.1 Dapivirine VR

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

6.3.2 Placebo VR

The placebo VR is manufactured with the same components as the drug-containing rings, except that it contains USP titanium dioxide dispersed in the silicone fluid as colorant, and no active pharmaceutical ingredient. The purpose of the colorant is for maintaining blinded conditions. The placebo VR should be stored at 15°C to 30°C.

6.4 Supply and Accountability

6.4.1 Supply

IPM (Silver Spring, MD) will oversee the manufacture all 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. If the participant is unable to attend their next scheduled visit it is up to the discretion of the IoR to provide an additional ring. Under special circumstances, more than two rings may be dispensed after consultation with the DAIDS MO. All such circumstances must be documented fully by the IoR/designee as described in the ASPIRE SSP Manual.

6.4.3 Accountability

Each CRS Pharmacist of Record (PoR) is required to maintain complete records of all study products received from the NIAID Clinical Research Products Management Center (CRPMC) 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-020 Pharmacy Manual

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

6.4.4 Retrieval of Study Product

As per Section 8, study product use for a participant may be temporarily held or permanently discontinued. Study product must be retrieved (optimally within 24 hours) and returned to the clinic when product use is permanently discontinued for HIV seroconversion (see table below). Additional study product retrieval specifications in response to product holds, discontinuations for other reasons, or IoR instruction, can be found in 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 3: Retrieval of Study Product

	Retrieve Study Product
Permanent discontinuation or temporary hold due to potential HIV seroconversion	Within 24 hours
Permanent discontinuation due to severe (Grade 3 or higher) renal or hepatic toxicity	Within 5 working days
Permanent discontinuation for any other reason	Within 5 working days
IoR discretion	Within 5 working days
Temporary hold due to pregnancy	Within 5 working days
Temporary hold for reasons other than pregnancy with expected duration of at least 7 days	Within 7 working days

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

It is not necessary to retrieve study products from participants for whom study product use is being temporarily held for less than 7 days. However, study products may be retrieved from such participants, to protect their safety, if there is concern that the participant may not comply with clinic staff instructions to refrain from study product use for the duration of the temporary hold. For all study product holds requiring retrieval of study product(s), if the study product(s) are not retrieved within timeframe stated in table above, the MTN-020 PSRT must be informed.

If prolonged use (greater than 35 days) of the study VR has occurred, the product must be retrieved.

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 supplies to this visit, study staff must arrange to retrieve the VR within 2 business days. If the study product(s) are not retrieved within that timeframe, the MTN-020 PSRT must be informed.

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

6.5 Adherence Counseling and Assessment

Counseling

Participants will receive study VR adherence counseling and product use instructions at the Enrollment Visit and at additional follow-up visits, as needed. Site staff will counsel participants in VR product use; including, to refrain from removing the ring (except as directed), and instructions for re-insertion in case of accidental ring expulsion, etc. Participants will also be discouraged from using intravaginal medications and practices as described in Section 6.7.

An Adherence Strengthening Approach, similar to that developed for the VOICE trial, will be adapted for ASPIRE.

Assessment

Participant behaviors regarding study VR use will be collected via standardized questions developed by the protocol team in conjunction with study site staff and community representatives, to maximize the accuracy of self-reported data. Assessment of participant adherence will be evaluated using a quantitative instrument.

6.6 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.

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

6.7 Use of Intravaginal Medications and Practices

Concomitant use of non-study vaginal products, practices or use of other devices including but not limited to spermicides, diaphragms, contraceptive VRs, vaginally applied medication, menstrual cups, cervical caps, douches, lubricants, etc., will be discouraged. Participants will be instructed to avoid these medications and practices in

order to protect the integrity of the lower genital tract and reduce the possibility of AEs due to agents other than the study ring and product.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is provided in Appendix I. Follow-up study visits may take place either 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 as soon as possible for a pelvic exam. 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 ASPIRE Study Specific Procedures (SSP) Manual available at www.mtnstopshiv.org.

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 28 days prior to the Enrollment Visit. Multiple visits may be conducted within this time period to complete all required screening procedures, if necessary. Written informed consent 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 4: Screening Visit

Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent for screening • Assign a unique Participant Identification (PTID) Number • Assess eligibility • Collect locator information • Provide reimbursement • 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 • Prescribe contraceptives*† • Conduct a physical examination • Perform a pelvic exam • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – human chorionic gonadotropin (hCG) – Urine culture*† – Nucleic Acid Amplification Test (NAAT) for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (GC/CT)
	Blood	• Collect blood – HIV-1 serology – Complete blood count (CBC) with platelets – Chemistries – Syphilis serology
	Pelvic	• Collect pelvic specimens – Rapid test for Trichomonas – Herpes lesion testing*† – Vaginal fluid pH*† – Potassium hydroxide (KOH) wet mount for candidiasis*† – Saline wet mount for *Bacterial vaginosis* (BV)*† – Pap smear interpretation*
Study Product/ Supplies		• Provision of study specified condoms

* if indicated, † per local standard of care

7.3 Enrollment Visit (Day 0)

Please note, if the potential participant is menstruating at this visit, the entire visit should be rescheduled for two days after completion of menses, but must be completed within 4 weeks of the Screening Visit.

In addition, all enrolled participants will receive regular individual HIV counseling, condoms, risk reduction counseling, and treatment for STIs as part of their clinic visits. If, during the course of the study, other new prevention strategies are found to be efficacious and are incorporated into national HIV prevention policies (e.g., tenofovir PrEP), 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 5: 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 • Schedule next study visit
Behavioral		• Conduct behavioral assessment, which will include sexual activity, condom use and intravaginal practices • Provide counseling – Contraceptive – HIV/STI risk reduction – HIV pre- and post-test – Protocol adherence, including VR adherence
Clinical		• Update medical and menstrual history • Update concomitant medications • Provide contraceptives*† • Conduct a physical examination • Perform a pelvic exam • Disclosure of available test results • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – Urine culture*† – NAAT GC/CT*†
	Blood	• Collect blood – Plasma archive – HIV-1 serology

	Pelvic	• Collect pelvic specimens – Gram stain – Vaginal fluid pH – Endocervical swab – Rapid test for Trichomonas*† – Herpes lesion testing*† – KOH wet mount for candidiasis*† – Saline wet mount for BV*†
Study Product/Supplies		• Provide study specified condoms • Provision of VR use instructions; including what to do in cases of ring expulsion or allergic reaction • Provision of one study VR for insertion • Demonstrated attempt to remove and reinsert the ring – Digital exam by clinician to check VR placement • Participants may also receive a bottle of water with which to rinse the study ring in the event of a ring expulsion, at select sites with capacity*

* if indicated, † per local standard of care

7.4 Follow-up Visits

7.4.1 Monthly, Quarterly, Semi-Annual Study Visits

The procedures listed below will occur monthly for the duration of follow-up.

Table 6: Follow-up Visits: Monthly, Quarterly, Semi-Annually

Follow-up Visits: Monthly, Quarterly, Semi-Annually	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Provide reimbursement for study visit • Schedule next visit
Behavioral	• Adherence assessment • Conduct behavioral assessment, which will include sexual activity, condom use, and intravaginal practices • Acceptability assessment • Conduct social harms assessment • Provide counseling (modified, if necessary) – Contraceptive – HIV/STI risk reduction – HIV pre- and post-test – Protocol adherence, including VR adherence
Clinical	• Review/update medical and menstrual history • Review/update concomitant medications • Provide contraceptives*† • Perform physical examination* • Perform pelvic examination for the collection pelvic specimens and to assess local safety* • Disclosure of available test results • Record/update AEs • 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 – CBC with platelets◔ – Chemistries◔ – Syphilis serology* – Plasma ◔
	Pelvic	• Collect pelvic specimens – Vaginal fluid – Rapid test for Trichomonas ◗ *† – Vaginal pH ◗ *† – Gram stain ◗ – Endocervical swab ◗ – Herpes lesion testing*† – KOH wet mount for candidiasis*† – Saline wet mount for BV*†
Study Product/Supplies		• Provision of study specified condoms • Provision of VR use instructions; including what to do in cases of ring expulsion or allergic reaction* • Participant or clinician/designee to remove used study VR • Collection of used study VR • Provision of study VR for insertion – Digital exam by clinician to check VR placement▲* • Bottle of water with which to rinse the study ring in the event of a ring expulsion, at select sites with capacity*

◔ = to be completed at all quarterly visits (Months 3, 6, 9, etc.), ◗ = to be completed at all semi-annual visits only (Months 6, 12, 18, etc.), * if indicated, † per local standard of care, ▲required at Month 1

7.4.2 Product Use End Visit (PUEV)

Table 7: PUEV

PUEV		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit
Behavioral		• Behavioral assessment, which will include sexual activity, condom use and intravaginal practices • Adherence assessment • Acceptability assessment • Social harms assessment • Provide counseling (modify, if necessary) – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Provide contraceptives*† • Perform physical examination • Perform pelvic examination • Disclosure of available test results • Record update AEs • 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 – Vaginal pH – Gram stain – Endocervical swab – KOH wet mount for candidiasis*† – Saline wet mount for BV*† – Rapid test for Trichomonas*† – Herpes lesion testing*† – Pap smear interpretation
Study Product		• Provision of study specified condoms • Participant or clinician/designee to remove used study VR • Collection of used study VR

* if indicated, † per local standard of care.

7.4.3 Study Exit/Termination Visit

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

Table 8: 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		• Behavioral assessment, which will include sexual activity, condom use and intravaginal practices • Provide counseling – HIV/STI risk reduction – HIV pre- and post-test
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Provide contraceptives*† • Disclosure of available test results • Perform pelvic examination* • Record/update AEs • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – hCG – Urine culture*† – NAAT for GC/CT*†
	Blood	• Collect blood – HIV-1 serology – Plasma
	Pelvic	• Collect pelvic specimens – Vaginal fluid – Vaginal pH*† – KOH wet mount for candidiasis*† – Saline wet mount for BV*† – Rapid test for Trichomonas*† – Herpes lesion testing*†
Study Product		• Provision of study specified condoms

* if indicated, † per local standard of care

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

7.5.1 Participants Who Become Infected with HIV-1

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-1 while on study product will be offered enrollment in MTN-015, the MTN Seroconverter Study. Participants are offered

enrollment in MTN-015 (www.mtnstopshiv.org) at the visit when seroconversion confirmation test results are discussed with the participant.

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

- HIV serology, HIV pre- and post-test counseling
- Provision of VR, instructions, product adherence counseling
- Complete blood count with platelets
- Chemistries
- Plasma/vaginal fluid sampling
- Scheduled ASPIRE Study Exit/Termination Visit

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

- Plasma
- CD4+ T cell count
- HIV-1 RNA PCR

The aforementioned procedures are done at the following time points:

- The visit (scheduled or interim) at which the participant is given her Western Blot or HIV RNA/DNA test results confirming her HIV-infection
- The 1st, 3rd, 6th, 12th, and 18th scheduled ASPIRE visit after the participant is informed of her HIV-infection.

Please reference the SSP for additional details (www.mtnstopshiv.org).

7.5.2 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. 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 examinations, including vaginal fluid collection, after 24 weeks of pregnancy

A participant who becomes pregnant during the course of study participation may be offered participation in MTN-016, the Prevention Agent Pregnancy Exposure Registry, see Section 7.9 for additional details.

7.5.3 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

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

7.5.4 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, e.g., a participant may need an addition VR or want to discuss problems with adherence to product use.
- In response to AEs. When interim contacts or visits are completed in response to participant reports of AEs, 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 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.

Interim visits will occur when more than one visit takes place within an allowable visit window. All interim contacts and visits will be documented in participants' study records and on CRFs, if applicable.

7.6 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.

7.7 Behavioral Evaluations

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

- VR adherence
- VR acceptability
- Sexual activity, including frequency of vaginal and anal sex; condom use; and intravaginal practices

Adherence Assessments
Adherence will be measured at all monthly visits including the final product use visit via questions about duration that the ring is out of the vagina and reasons for expulsion and removal.

Acceptability Assessments
Acceptability will be measured at all scheduled quarterly visits including the final product use visit via questions about discomfort due to the VR, feeling the VR during daily activity and sex, ease of insertion and removal, partner awareness of VR during sex, self and partner attitudes towards the VR.

Sexual activity, condom use and intravaginal practices
These behaviors will be measured at all scheduled quarterly visits, including the final product use visit.

7.8 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 ASPIRE SSP Manual.

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

7.9 Laboratory Evaluations

<u>Local Laboratory</u>

- Urine
    - hCG
    - Urine culture
    - NAAT for *GC/CT*

- Blood
  - Plasma archive (stored at site until notified by MTN Network Laboratory (NL))
  - Plasma (stored at site until notified by MTN NL)
  - Syphilis
  - HIV serology
  - CBC with platelets
  - Chemistries
    - Creatinine, AST, ALT
- Pelvic
  - Rapid test for Trichomonas
  - Vaginal fluid for wet mount microscopy (saline wet mount for BV; KOH for candidiasis)
  - Herpes lesion testing
  - Vaginal fluid pH

Network Laboratory

- Blood
  - HIV-1 confirmatory testing as needed (see Appendix III)
  - Drug concentration in vaginal fluid and blood

- Pelvic
  - Gram stain assessment of vaginal fluid slides
  - Vaginal fluid
  - PK assessments on vaginal fluid
  - Endocervical swab

7.10 Primary HIV-1 Endpoint Determination

All study sites will perform HIV testing per the algorithm in Appendix III for purposes of primary 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 (www.mtnstopshiv.org). 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 NL; at each testing time point when rapid tests are used at least one FDA-approved rapid test kit is used. All Western blot testing is performed using FDA-approved test kits.

The MTN NL will verify HIV testing performed at the study site laboratories for purposes of eligibility determination and primary outcome ascertainment as follows:

- The NL will test Study Entry, PUEV, and scheduled Study Exit/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 Visit(s). If any false-negative local laboratory

results are identified, the NL will test the respective Study Entry, PUEV and scheduled Study Exit/Termination Visit specimens from all enrolled participants from that Clinical Research Site.

- The NL 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 NL 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 7.5.1. All specimens will be tested for evidence of HIV infection using FDA-licensed tests. For seroconverters, Study Entry specimens also will be tested by RNA PCR.

NL 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.

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 Manual of Operational Procedures (MOP) for detailed information on the composition, roles, and responsibilities of the endpoint adjudication committee (www.mtnstopshiv.org).

7.11 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), the MTN Network Laboratory Manual (www.mtnstopshiv.org), in accordance with current DAIDS Laboratory Requirements, ASPIRE Study Specific Procedures Manual (www.mtnstopshiv.org), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

7.12 Specimen Handling

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

7.13 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the 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. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

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

The National Institute of Allergy and Infectious Diseases (NIAID) Prevention Trials Data and Safety Monitoring Board (DSMB) monitors participant safety throughout the study. The DSMB meets routinely, see Section 10.7.2 for additional details. At the time of these reviews, or at any other time, the DSMB may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

8.2 Adverse Events Definitions and Reporting Requirements

8.2.1 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 both study products.

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

- All genital, genitourinary, and reproductive system AEs
    - 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.

8.2.2 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.

8.2.3 Adverse Event Relationship to Study Product

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

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

8.3 Expedited Adverse Event Reporting Requirements

8.3.1 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).

8.3.2 Reporting Requirements for this Study

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

8.3.3 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 8.2.1. 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/.

8.3.4 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).

8.4 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 is 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 ASPIRE 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.

8.5 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 VR product use by the IoR/designee for any of the following reasons:

- Acquisition of HIV-1 infection; such participants will not resume product use at any time. The study VR 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-1 infection is confirmed.
- Allergic reaction to the 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 termination of the pregnancy, 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 product management if improvement to severity ≤ Grade 2 cannot be documented within 2 weeks.

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

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

9.5 Genital Sexually Transmitted Infection, Reproductive Tract Infection and Other Clinical Findings

The IoR/designee should manage STI/RTI per local guidelines or current WHO guidelines, available at http://www.who.int/en/. Observed single dose treatment should be provided whenever possible. Vaginally applied medications should not be used, except that vaginal azoles should be used to treat symptomatic candidiasis among pregnant women.

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 to avoid intravaginal medication use.

- 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 participant between scheduled visits, an interim visit may be scheduled at the discretion of the site investigator. Management of genital events observed at scheduled or interim visits will be in accordance with the following:

Superficial epithelial disruption (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)

- Remove study VR for deep epithelial disruption confirmed by site investigator
- Re-evaluate in 3-5 days and reinstate study VR use if resolved
- If unresolved at 3-5 days, re-evaluate within 2-3 days. If resolved at that time, may reinstate 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

- Remove study VR
- Perform naked eye evaluation
- Re-evaluate in 3-5 days and reinstate study VR use if resolved
- If unresolved at 3-5 days, re-evaluate within 2-3 days. If resolved at that time may reinstate 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)

- Remove 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 and consult PSRT
- If GC/CT is not detected, reevaluate in 3 days. If all symptoms and signs are resolved at that time continue study VR use

Genital petechia(e)

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

Genital ecchymosis

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

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-1 Infection

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

At every study visit, study staff will actively follow-up on prior referrals to HIV-1 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 NL 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, after consultation with the PSRT. 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 is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume product use (if applicable) and follow-up through their originally scheduled study exit date, pending consultation with the PSRT.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is a Phase 3, multi-site, randomized, double-blinded placebo-controlled trial. A total of approximately 3476 participants will be randomly assigned in a 1:1 ratio to either dapivirine VR or placebo VR.

It is estimated that 120 endpoints will be reached approximately 24 months from the start of randomization, allowing for a loss to follow-up rate of 1%/month. Based on the expected HIV-1 baseline incidence rates at the sites, the accrual and follow-up plan should achieve the target of 120 HIV-1 seroconversions needed for appropriate statistical power for the study primary objectives.

10.2 Study Endpoints

10.2.1 Primary Endpoints

- **Effectiveness**

  - HIV-1 infection as measured by seroconversion at the end of the investigational product use period with seroconversion defined by the algorithm in Appendix III

- **Safety**

  - Grade 2 AEs judged to be related to study product
  - Grade 3 and 4 AEs
  - All serious adverse events

10.2.2 Secondary Endpoints

- **Acceptability**

  Consistent with the secondary objective to evaluate the acceptability of the study VR (dapivirine or placebo) in HIV-uninfected women, when inserted once every 4 weeks over the investigational product use period, the following secondary endpoint will be assessed:

  - Participant report of participant and partner-related acceptability including (dis)comfort, ring insertion and removal/ expulsion issues, change in sexual feelings, willingness to use in the future

- **Adherence**

  Consistent with the secondary objective to evaluate the adherence to the study VR (dapivirine or placebo) in HIV-uninfected women, when inserted once every 4 weeks over the investigational product use period, the following secondary endpoint will be assessed:

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

- **HIV-1 Drug Resistance**

  Consistent with the secondary objective to assess the occurrence of HIV-1 drug resistance in women who acquire HIV-1 infection while using study product, the following secondary endpoint will be assessed:

- HIV-1 drug resistance mutations among participants who acquire HIV-1 infection

- **Drug Concentration Data**

  Consistent with the secondary objective to evaluate the relationship between drug concentration and HIV-1 seroconversion, the following secondary endpoint will be assessed:

  - Steady-state drug concentrations in blood and vaginal fluid

10.3 Sample Size and Power Calculations

10.3.1 Primary Endpoint

To achieve an overall effect of preventing HIV-1 infection at the population level, a minimum bound greater than 0% for the effectiveness in individual efficacy trials needs to be achieved to offset any negative indirect effects potentially induced by an increase in risky behavior (e.g., sexual disinhibition) and/or in changes in condom usage. Indeed, mathematical modeling has shown that for an HIV vaccine to be effective at the population level, the minimum (direct) efficacy may need to be 30% or greater. [16,27] Recently, similar mathematical models suggest that the (direct) efficacy of oral PrEP should be above 25-50%. Similarly, the (direct) efficacy of vaginal microbicides may also need to be above 25-50% to offset potential changes in condom usage.[28,29]

Based on this, several of the ongoing or planned oral PrEP trials are powered to rule out a lower effectiveness between 10% and 30%. The protocol team has set the minimum lower bound for the effectiveness of the study product at 25%. Therefore the null hypothesis is that the active product will be no more than 25% effective. That is, the trial is powered to detect effectiveness of at least 60% and to rule out effectiveness of 25% or lower.

The sample size calculation follows directly from Fleming and Harrington, 1991, pages 394-395 with a variance inflation adjustment for null and alternative relative risks outside the range 0.5-2.0.[30] Here, the null relative risk is 0.75, while the alternative is 0.40. The formula for calculating the required number of events is:

$$L = \left(\frac{Z_{0.9} - Z_{0.025}}{(\ln R_0 - \ln R_1)\ (2\ \overline{VIF})} \right)^2,$$

where $VIF = \frac{1+R_0}{8R_0}^2 + \frac{1+R_1}{8R_1}^2$, $R_0$is the relative risk under the null hypothesis and R_1 is the relative risk under the alternative hypothesis.

With $R_0 = 0.75$ and $R_1 = 0.40$, the formula above indicates that a trial with 120 events would provide 90% power to detect a minimum 60% reduction in risk of HIV-1 infection

while ruling out a 25% or smaller reduction using a log-rank test having a one-sided positive error rate of 0.025.

In HTPN 035,[31] HIV incidence rates in the 0.5% PRO2000 Gel, BufferGel, Placebo Gel and No Gel arms were 2.7, 4.1, 3.9 and 4.0 per 100 women-years, respectively. In this study design, we choose 3.9% to be consistent with the lower estimate of the two placebo arms in HPTN 035. We expect this may be a conservative estimate of incidence. Studies in similar settings saw higher incidence rates including FEM-PrEP (5%/year) and CAPRISA 004 (9.1%/year). Assuming an annual infection rate of 3.9% in the placebo arm, the trial must include 4396 person-years of follow-up.

10.4 Participant Accrual, Follow-up and Retention

Assuming participants are accrued according to the figure below for a total of 3476 participants and an annual overall infection rate of 2.73%, it would take approximately 24 months from the start of randomization to reach the required 120 endpoints. This calculation allows for a loss to follow-up rate of 1% per month.

Month of study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Number enrolled	25	75	150	200	275	350	400	400	400	400	400	400

Figure 1: Projected Enrollment Used for Study Design

Periodically during the 12-month accrual period, the MTN SMC, DSMB, and/or the Protocol Team will review performance data from each study site — including accrual rates, retention rates, protocol adherence measures, data quality measures, and HIV-1 incidence rates — to determine whether enrollment slots should be shifted across sites to achieve the study objectives more efficiently and to determine when to discontinue accrual. The Protocol Team will make every effort to discontinue accrual approximately 12 months prior to when the targeted number of incident HIV-1 infections (i.e., n=120) will be observed.

It is expected that follow-up will be completed at 24 months from the start of randomization, not including the approximate 4 week period between the scheduled PUEV and Study Exit/Termination Visit.

Note that 99% retention per month (~89% per year) is used to be conservative for the sample size calculations; however retention of 95% per year will be the target.

The assumed HIV-1 seroincidence rates are averages of best available estimates based on ongoing or recently completed research studies and/or other available epidemiologic information from populations as similar as possible to the study population. In particular, estimates from populations receiving condom counseling were used when available.

10.5 Randomization

Participants will be randomized in a 1:1 ratio to the two arms of the study. Study arm randomization will be stratified by site to ensure balanced assignment for products at each site. The randomization scheme will be generated and maintained by the MTN SDMC. Assignment of randomization is considered the effective act of participant enrollment.

10.6 Blinding

Both study staff and participants will be blinded to the random assignments of participants to the study treatment arms. Within the active and placebo arm, study products are supplied in identical packaging. Randomization documentation and other pharmacy records will be stored in a secure location in the site pharmacy (apart from the rest of the participant file). This information must not be accessible to study staff members who complete other study procedures with participants. Blinding will be maintained until all data are entered into the study database, all study endpoint data and other data included in the final analysis have been cleaned and verified, and the data are ready for final analysis. This will be explained to participants as part of the informed consent process. There are no circumstances under which it is expected that unblinding will be necessary for provision of medical treatment or to otherwise protect the safety of study participants. As described in Section 9, in the event that an IoR/designee is concerned that a participant might be put at undue risk by continuing product use, the IoR/designee may discontinue product use by this participant, however knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an IoR/designee feels that specific product knowledge is necessary to protect participant safety, the IoR/designee will notify the PSRT to consider and rule upon the request. In the event of a serious adverse event requiring submission as an expedited Individual Case Safety Report to regulatory authorities, unblinding information for the specific participant will be provided to DAIDS by SCHARP. The DSMB will be provided with unblinded product coding information with closed study reports upon request.

10.7 Data and Safety Monitoring Procedures

10.7.1 Study Monitoring Committee

In addition to the safety monitoring done by the PSRT, the MTN SDMC will prepare study progress reports for review by the MTN SMC. The SMC will conduct interim reviews of study progress (pooled over study arms), including rates of participant accrual, retention, rates of adherence to study product, and HIV-1 rates. These reviews will take place approximately every 6 months, or as needed. Typically, as much as possible, a SMC review is planned 2 – 4 weeks prior to a DSMB review such that recommendations from the SMC may be passed along to the DSMB. This process allows the DSMB to focus less on trial operational issues and more on safety. However,

all data presented to the SMC will also be presented to the DSMB. 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.

Based on the assumptions of Section 10.3, the target HIV-1 seroconversion rate is 2.73% for the entire trial. If the observed HIV-1 rate is substantially lower or higher than expected, the protocol team may need to develop plans for adjusting the accrual and/or the length of follow-up (see Section 10.4). Based on prior performance the sites have adequate additional capacity to effectively respond to seroincidence rates much lower than those initially used for the power calculations.

Note that the monitoring of the trial target HIV-1 rate as described above was successfully implemented in HPTN 035. Further monitoring of the HIV-1 rates will be performed by the DSMB, which will ensure that the target number of primary endpoints will be achieved.

10.7.2 Data and Safety Monitoring Board (DSMB)

DSMB reviews of study safety data will be conducted approximately every six to twelve months. A no-data DSMB meeting will be scheduled prior or close to study initiation where the protocol and the complete interim monitoring plan will be presented to the DSMB members. At subsequent DSMB reviews, besides safety and efficacy data presentations, tables will be prepared for these reviews to assess the study conduct operational characteristics (e.g., accrual, adherence, retention, HIV-1 incidence). That information will be compared to the protocol assumptions, and alterations will be made to the study design (e.g., increase or decrease in accrual and/or follow-up and/or number of sites) if recommended by the DSMB.

10.7.3 Monitoring Quality of Study Conduct Operational Characteristics and Implementation

The study may be terminated or modified for poor accrual/recruitment, adherence/product use, retention, and/or low HIV-1 acquisition rate. Regular reports will be provided to the DSMB and SMC that outline the potential impact on the study's ability to detect a difference between the treatment arms if there are deviations from the statistical design in terms of accrual/recruitment, adherence/product use, retention, and/or low HIV-1 acquisition rate.

10.7.4 Monitoring of Safety and Efficacy Endpoints

The DSMB may recommend early termination of the study or modification when there is clear evidence of benefit, futility, or harm, or may recommend continuation of the study if the balance between potential benefit and harm remains adequate. Therefore, the DSMB may recommend stopping or modifying the study early in the following situations:

- Clear evidence of serious safety problems including:
    - An excess in frequency of any AEs (judged by the DSMB to be harmful to the participants) in the active product arm.
    - An excess in frequency of any SAEs (Grade 4 and higher) in the active product arm.
    - An excess in frequency of the primary safety endpoints as defined in Section 10.2.1 in the active product arm.

- Clear evidence of benefit/harm:
    - A statistically significant difference in the rate of HIV-1 infection between the active product arm and the placebo arm (appropriately adjusted for sequential monitoring of the trial)

        Efficacy will be monitored with a Type 1 error rate of 2.5% against a null hypothesis of 25% effectiveness.

        Harm will be monitored with a Type 1 error rate of 2.5% against a null hypothesis of 0% effectiveness.

- Clear evidence of futility:
    - Futility is defined to be results sufficient to rule out that the rate of HIV-1 infection in the active product arm is smaller than the rate of HIV-1 infection in the placebo arm leading to a lack of difference in the rate of HIV-1 infection between the two arms appropriately adjusted for the sequential monitoring of the trial.

        Note that the futility stopping rules will be based on a null hypothesis of no reduction (i.e., 0% effectiveness) with a false positive error rate of 2.5%. The rationale for this is the current lack of proof for VR effectiveness for women at risk of sexual acquisition of HIV-1. While the protocol team does strongly believe effectiveness of these interventions would need to rule out less than 25% effectiveness to be a viable public health intervention, demonstrated effectiveness > 0% that does not rule out 25% would still offer hope of a potentially effective prevention methodology, albeit needing further evaluation. Therefore, the protocol team would propose to the DSMB only stopping for futility if an intervention shows no evidence of reduction in HIV-1 infection rates.

Interim and final analyses will be adjusted to maintain an overall type I error rate. Adjustments will be based on Lan and DeMet's implementation of the O'Brien-Fleming grouped sequential stopping boundary with the time scale measured on the cumulative number of primary endpoints.[32] This implementation will permit early stopping only for very strong positive or negative effects and maintains nearly all of the nominal power for the final analysis.

The DSMB may request additional analyses of the safety, toxicity, and/or effectiveness data from this study. The Statistical Analysis Plan for this study will provide further details on the interim monitoring strategy including the specifics of the above guidelines for operational, efficacy, harm and futility and other relevant details.

10.8 Primary Analysis

When the use of descriptive statistics to assess group or site characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Typically, within-arm assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired t-test (for continuous variables). In general, when use of formal testing to assess differences between arms is required, the following methods will be used: for binomial response variables, chi-square tests and logistic regression; for continuous variables, t-tests and linear regression. To assess the adequacy of the randomization, participants will be compared for baseline characteristics including demographics, pelvic examination, and laboratory measurements using descriptive statistics.

10.8.1 Primary Safety Analysis

Incidence rates of safety and toxicity endpoints will be compared across the arms using Cox Proportional Hazards Models stratified by site with robust variance estimates.[33] For this analysis, a safety and toxicity endpoint is defined as the occurrence in a participant of any primary safety endpoint described in Section 10.2.1 during follow-up.

The above analysis only looks at the time until the first event in a participant. To include information about subsequent events, an analysis that allows recurring events in individual participants will be conducted. This analysis will be performed using the Andersen Gill Proportional Hazards Model stratified by site with robust variance estimates.

AEs 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 *p*-value and confidence interval for the relative risk (active product: placebo) of each AE will be calculated, as well as the difference in rates between treatment groups (active product – corresponding placebo) and its confidence interval. To safeguard against too many "false positive" safety findings, the statistical significance of the *p*-values will be assessed after a multiplicity adjustment. [34] 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.

Boxplots of local laboratory values will be generated for baseline values and for values measured during the course of the study. Each boxplot will show the 1st quartile, the median, and the 3rd quartile. Outliers, or values outside the boxplot, will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

Note that all of the above analyses will be conducted under the 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 in the active product arms. 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.

10.8.2 Primary Effectiveness Analysis

The primary analysis will be performed under the ITT principle with time from randomization to seroconversion as the endpoint. Cox Proportional Hazards models stratified by site will be used to assess the effectiveness of the VR. Product effectiveness will be expressed as a percent reduction in the HIV-1 incidence rate (i.e., 100 x [1 – (active product HIV-1 infection rate / corresponding placebo HIV-1 infection rate)]).

10.9 Analysis of Main Secondary Endpoints

10.9.1 Acceptability

Information about acceptability will be obtained from questionnaires in which the participants will rate acceptability on a combination of categorical and continuous scales. Continuous measures of acceptability will be compared across arms using a t-test while categorical measures will be compared using chi-squared tests. Additional exploratory analyses of acceptability will be conducted to compare the intersection of acceptability of the product in some areas versus others and to determine if an appropriate composite measure of acceptability can be constructed.

10.9.2 Adherence

The adherence analysis will include:

1. Estimation of VR expulsion and removal rates
2. Estimation of the cumulative duration of time that the ring is out of the vagina
3. Comparison between arms of the quantities estimated in 1 and 2
4. Estimation of trends over time in adherence rates
5. Exploration of reasons for ring removal

The primary adherence analysis will focus on 1-3 using descriptive statistics for within arm estimation and t-tests to compare means or bootstrap-based tests to compare medians across arms. Trends over time in adherence rates will be explored using generalized estimating equations (GEE). Reasons for ring removal will be tabulated.

10.9.3 Drug Resistance

Rates of drug resistance in women who seroconvert during the study will be estimated and compared across arms. Fisher's Exact test will be used to compare rates of drug resistance across the arms at single points in time. GEE will be used to explore trends in resistance over time.

10.9.4 Pharmacokinetics

Plasma and vaginally sampled fluid dapivirine concentrations, will be used to describe the steady-state dapivirine concentrations at specified times throughout the study. Relationships between research participant characteristics will be explored, including study site, height, weight, adherence, and medical co-morbidities. Participant-specific dapivirine concentrations in each biological matrix will be explored for relationship to seroconversion outcomes.

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.

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.

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 study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, SDMC, and NL; 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 are forwarded to DAIDS for cross-referencing with other INDs for the study products. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement executed by NIAID and IPM.

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

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

13.4 Risk Benefit Statement

13.4.1 Risks

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

Use of the study VR may lead to vaginal symptoms, including irritation, increased discharge, and discomfort (including with vaginal intercourse). It is possible that a participant may have an allergic reaction to the study product.

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

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

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

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

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

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical examination, pelvic examination, and routine laboratory testing. Participants 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

Written informed consent will be obtained from each study participant prior to both screening and enrollment. Written informed consent also will be obtained for long-term specimen storage and possible future testing as well as for off-site clinic visits as needed. Neither consent for long-term specimen storage nor off-site study visits are required for study participation. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://rsc.tech-res.com/policiesandregulations/). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

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

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

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

13.6 Participant Confidentiality

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

All study-related information will be stored securely 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 separate, locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the US Federal Government, including the US FDA, the US OHRP, NIH, and/or contractors of the NIH, and other local and US regulatory authorities
- Representatives of IPM
- 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 7.5.2. 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 among 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.

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 emphasize the unknown efficacy of the study products in preventing HIV-1 infection. In accordance with the policies of the NIH, participants must receive their HIV-1 test results to take part in this study. Condoms will be provided 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 NIAID, the MTN, IPM, the US FDA, the OHRP, other government or regulatory authorities, or site IRBs/ECs.

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies and a clinical trial agreement (CTA) between IPM and NIAID will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS, National Institute of Mental Health (NIMH), and IPM for review prior to submission.

15 APPENDICES

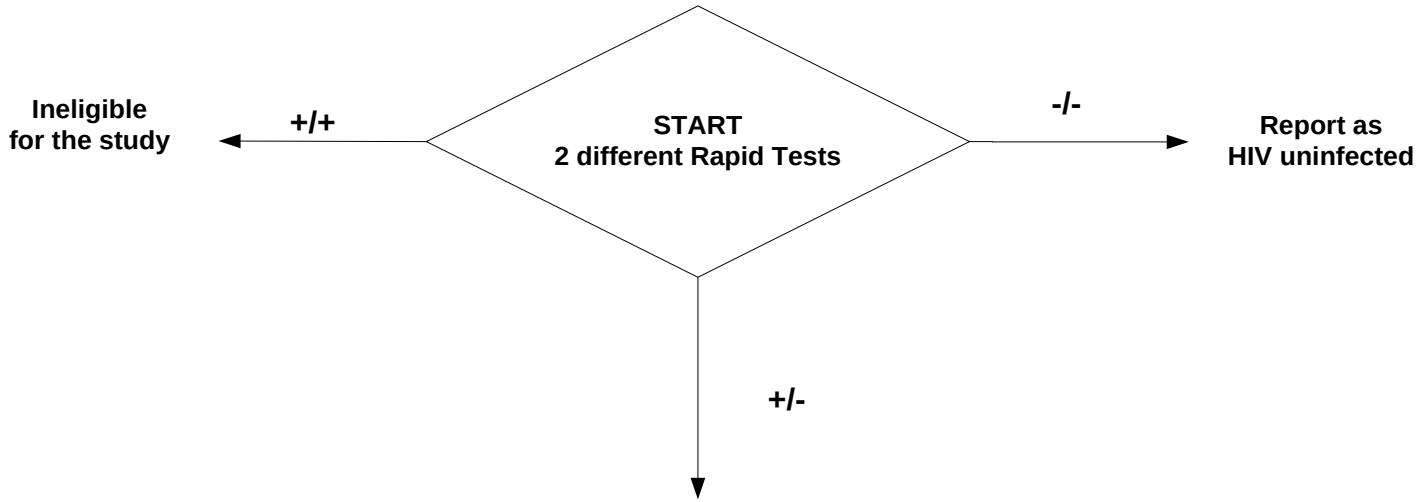
APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

		SCR	ENR	Monthly Visits	Quarterly Visits	Semi-Annual Visits	PUEV	Study Exit/ Term. Visit
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	X
Randomization			X					
Provide reimbursement		X	X	X	X	X	X	X
Schedule next visit		*	X	X	X	X	X	*
BEHAVIORAL								
Contraceptive counseling		X	X	X	X	X		
Protocol adherence, including VR adherence counseling			X	X	X	X		
HIV/STI risk reduction counseling		X	X	X	X	X	X	X
HIV pre- and post-test counseling		X	X	X	X	X	X	X
Conduct a behavioral assessment includes sexual activity, condom use, and intravaginal practices			X		X	X	X	X
Conduct an adherence assessment				X	X	X	X	
Conduct an acceptability assessment					X	X	X	
Conduct social harms assessment					X	X	X	
CLINICAL								
Obtain/update medical and menstrual history		X	X	X	X	X	X	X
Obtain/update concomitant medications		X	X	X	X	X	X	X
Conduct a physical examination		X	X	*	X	X	X	
Perform a pelvic exam		X	X	*	*	X	X	*
Prescribe contraceptives		*†	*†	*†	*†	*†	*†	*†
Disclose available test results			X	X	X	X	X	X
Record/update AEs				X	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	X
	Urine culture	*†	*†	*†	*†	*†	*†	*†
	NAAT for GC/CT	X	*†	*†	*†	X	*†	*†
BLOOD	HIV-1 Serology	X	X	X	X	X	X	X
	CBC with platelets	X			X	X	X	
	Chemistries	X			X	X	X	
	Syphilis serology	X		*	*	*	X	
	Plasma		◊		X	X	X	X

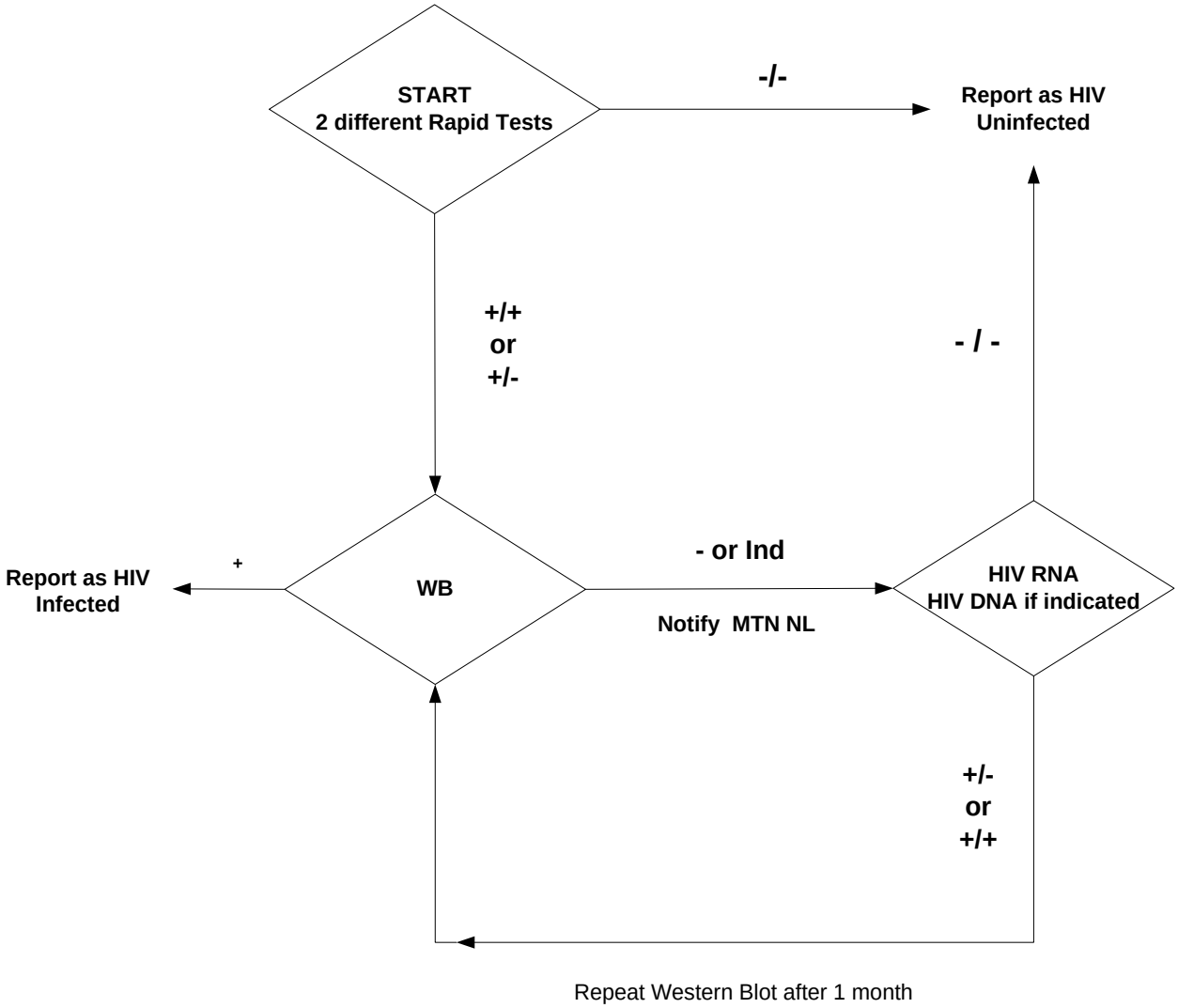
		SCR	ENR	Monthly Visits	Quarterly Visits	Semi-Annual Visits	PUEV	Study Exit/ Term. Visit
PELVIC	Rapid test for Trichomonas	X	*†	*†	*†	X	*†	*†
	Herpes lesion testing	*†	*†	*†	*†	*†	*†	*†
	Vaginal fluid pH	*†	X	*†	*†	X	X	*†
	KOH wet mount for candidiasis	*†	*†	*†	*†	*†	*†	*†
	Saline wet mount for BV	*†	*†	*†	*†	*†	*†	*†
	Gram stain		X			X	X	
	Vaginal fluid			X	X	X	X	X
	Pap Smear interpretation	*					X	
	Endocervical swab		X			X	X	
STUDY PRODUCT/ SUPPLIES								
Provision of study specified condoms		X	X	X	X	X	X	X
Provision of study VR instructions			X	*	*	*		
Provision of one study VR for insertion			X	X	X	X		
Participant or clinician/designee to remove used study VR				X	X	X	X	
Digital exam(s) by clinician to check VR placement			X	₪ *	*	*		
Demonstrated attempt to remove and reinsert the ring			X					
Collection of used study VR				X	X	X	X	
Dispense a bottle of water, at select sites with capacity			*	*	*	*		

X mandatory, * If indicated, † per local standard of care, ◊= for archive, ₪= required at Month 1

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



APPENDIX III: ALGORITHM FOR HIV ANTIBODY TESTING FOR FOLLOW-UP AND PRIMARY ENDPOINT



Ind: Indeterminate test results

APPENDIX IV: SAMPLE INFORMED CONSENT DOCUMENT (SCREENING)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-020
A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women

A Study to Prevent Infection with a Ring for Extended Use (ASPIRE)

Version 1.0

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 known as MTN-020: ASPIRE, *A Study to Prevent Infection with a Ring for Extended Use*. This study is for sexually active women between the ages of 18 and 45 years old. Approximately 3476 women will be in this study across many clinics in multiple countries in Africa. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). The products being used in this study include a dapivirine vaginal ring and a placebo vaginal ring; these products will be explained later in this document. These rings are supplied by the International Partnership for Microbicides (IPM). The person in charge of this study at this clinic is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to screen for this study, we want you to learn about the study.

Screening exams and tests, which include interview questions, urine, and blood tests, a physical exam and an exam 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.

YOUR PARTICIPATION IS VOLUNTARY
This consent form gives information about the screening tests that will be discussed with you. Once you understand the screening tests, and if you agree to take part, you will be asked to sign your name on this form. You will be offered a copy of this form to keep. Before you learn about the screening tests, 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
- Some people may not be able to join this study because of information found during the screening tests.
- 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.

- If you decide not to have the screening tests, you can still join another research study later, if one is available and you qualify. However, you cannot join the ASPIRE study if you are currently or have recently taken part (in the past 60 days) in another study that used drugs, medical devices or vaginal products.
- If you participated in the VOICE study or any other HIV prevention study using antiretroviral medications (pills or gel), within 12 months of your enrollment visit, you are not eligible to join ASPIRE
- 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.
- You will receive the results of the screening tests even if you are not eligible to join this study.
- 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 try to find out if a vaginal ring containing the medicine dapivirine is safe and effective in preventing the transmission of HIV-1. A vaginal ring is a flexible ring that may or may not contain the study drug, dapivirine. Researchers do not yet know if this ring will work in humans to protect against HIV. This is why we are doing this research. Women will place a ring in the vagina monthly for approximately 12-24 months; however this period could be shorter or longer than anticipated.

STUDY PRODUCTS

There are two different rings that will be used in this study. The first is a vaginal ring containing dapivirine. Dapivirine vaginal rings have been previously tested and found to be generally safe and well-tolerated 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. Drugs 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. The other ring in this study is a placebo vaginal ring, a placebo is a product that has no study drug in it.

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

STUDY GROUPS

If you meet the study requirements and if you decide to enroll in MTN-020, you will be in one of two vaginal ring study groups; dapivirine vaginal ring or placebo vaginal ring. Approximately 3476 women will be in this study, half of the women who participate in the study will receive a placebo vaginal ring the other half will receive the dapivirine vaginal ring. Women will be assigned to a group by random chance, like flipping a coin. Neither the women participating in this study nor the staff can decide which ring will be selected or know which ring participants have received.

Both of the study groups are important to this study. No matter which study group you are in, you must remember that we do not know if the dapivirine ring works to protect women from getting HIV.

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 are completed today. However if you have to come back to complete this visit, some procedures may need to be repeated. If you enroll in the study, you will have visits every month at *[sites to specify where visits will take place].*

Screening Visit:
If you agree, your first visit will happen today. Study staff will help you understand this form and answer your questions before you sign it. The procedures done at this visit will take about [sites to insert time].

- You will be asked questions about where you live and other questions about you, your medical health (including what medications you are taking), menstrual history, your sexual and vaginal practices and other questions to ensure you are eligible for this study. You will also be asked questions to make sure that you understand the study requirements.

- Study staff will:
  - Perform a physical exam
  - 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 for the safety of your baby. If the study is still open after your pregnancy, you may come back here to find out if you are eligible.
      - Talk about ways to avoid becoming pregnant, such as 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 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. The study staff will tell you about other studies you may be eligible for, if any.
      - If you are not HIV positive you will talk with study staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex.

  - 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. They may also take some fluids to test for other possible problems if they feel it is necessary.
    - The study staff may also collect samples from your cervix for a "Pap test". If the test shows a problem, it could mean you should have more tests. If you have a written report confirming a normal Pap test in the past 12 months or if you had an abnormal Pap test but had follow-up indicating no treatment was required, you will not need to have a Pap test 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

- Provide you with the results of your tests, if available

- Provide you with male condoms

- Schedule your next visit to enroll in MTN-020, if you are eligible and willing

Results of tests listed above will be available within [*Sites to specify timeframe*] of your visit. If you decide not to join MTN-020, no blood collected at this visit will be kept or used for any tests other than those listed above. The study staff will review your test results with you when they are available. If the results show you can join the ASPIRE 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 will stop 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.

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 or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out 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
You may receive no direct benefit from the screening tests. However, 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 to not 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 are 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. 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 specify 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.

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 below.

_____	_____	_____
Participant Name (print)	Participant Signature	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, NIH

MTN-020
A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women

A Study to Prevent Infection with a Ring for Extended Use (ASPIRE)

Version 1.0

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

INFORMED CONSENT
You are being asked to take part in MTN-020: ASPIRE, *A Study to Prevent Infection with a Ring for Extended Use*. This study is for sexually active women between the ages of 18 and 45 years old. Approximately 3476 women will be in this study across many clinics in multiple countries in Africa. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). The products being used in this study include a dapivirine vaginal ring and a placebo vaginal ring; these products will be explained later in this document. These rings are supplied by the International Partnership for Microbicides (IPM). The person in charge of this study at this clinic is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. 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. You may decide not to join or to withdraw from the study at any time.

YOUR PARTICIPATION IS VOLUNTARY
Once you read, discuss, and understand the study, and if you agree to take part, you will be asked to sign your name on this form. You will be offered a copy of this form to keep.

PURPOSE OF THE STUDY
This research study will try to find out if a vaginal ring containing the drug dapivirine is safe and effective in preventing the transmission of HIV-1. Researchers do not yet know if this ring will work in humans to protect against HIV. This is why we are doing this research. Women will place a ring in the vagina monthly for approximately 12 months to 24 months. The vaginal rings used in this study are flexible rings that may or may not contain the study drug, dapivirine.

STUDY PRODUCTS
There are two different rings that will be used in this study. The first is a vaginal ring containing dapivirine. Dapivirine vaginal rings have been previously tested and found to be generally safe and well-tolerated 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. Drugs 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. The other ring in this study is a placebo vaginal ring; a placebo is a product that has no study drug in it.

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

STUDY GROUPS

If you meet the study requirements, and, if you decide to enroll in MTN-020, you will be in one of two vaginal ring study groups; dapivirine vaginal ring or placebo vaginal ring. A placebo vaginal ring is a ring that will look like the other rings but has no medicine in it. Approximately 3476 women will participate in this study, half of the women will be in each study group and women will be assigned to a group by random chance, like flipping a coin. Neither the women participating in this study nor the staff can decide which ring will be selected or know which ring participants have received.

You will be asked to place a ring in your vagina monthly and not remove it for a month; a study clinician can help you to insert the ring if you are unable to do so. After one month, you or the study clinician will remove the ring and replace it with a new ring. The ring should not be worn beyond 35 days, unless you are told otherwise by study staff. This will last for approximately 12-24 months; however this period could be shorter or longer than anticipated.

Both of the study groups are important to this study. No matter which study group you are in, you must remember that we do not know if the dapivirine ring works to protect women from getting HIV.

WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN THE ASPIRE STUDY?

If you decide to enroll in the study, some procedures will occur today. After today you will be in the study for 13-25 months. You will have a visit here today (Day 0), and monthly for up to 25 months. As previously mentioned, you will use a vaginal ring for 12- 24 months and after the ring is removed you will have a final study visit approximately 4 weeks after you finish using the ring to check on your health. Study visits may be required beyond the final study visit to monitor your health. Procedures done at these visits will take approximately *[site to insert].*

You will be randomly assigned by study staff to one of two study groups. Neither you nor study staff will know which group you are in, choose your group or change the group you have been placed into. Women in the study groups will have the same study visit schedule.

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 information about where you live and how we can contact you or update study staff with this information
- Describe any changes in your health (including what medicines you are taking) and your menstrual periods
- Describe any health problems or other problems having to do with the study including the vaginal ring since your last visit, except at your Enrollment Visit

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, including information about wearing the ring during menses, how to clean the ring if it falls out, etc.

- Receive and, if you are able, insert a new study ring at each visit. If you are not able a study clinician may help you insert/remove the study ring.

- Have an exam to ensure the ring is properly inserted.

- Return your vaginal ring to study staff

- *[The following may be omitted based upon local water quality:]* Receive a bottle of water to take home to wash off the ring in the event it falls out, if you are in a location where clean water is scarce and if you need it

- In the event that the ring falls out, you may return to the clinic to have the ring reinserted if you are uncomfortable doing so yourself

- Answer questions about your experience using the vaginal ring, including whether or not the ring was removed from or fell out of your vagina. Answer questions about any problems you may have had during your participation in this study. Also, you may be asked questions about vaginal practices that may affect how the study drug is absorbed by your body. Answer questions that may make you uncomfortable, such as 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 be asked to have the following clinical procedures performed:

- A physical exam

- 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 result as soon as it is 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 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 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.
    - If you were to become infected with HIV these samples would be processed to see how much study product is absorbed by your body.

- Provide a urine sample to:
    - Check to see if you are pregnant
    - Test for infections passed through sex

- Provide vaginal fluid samples:
    - To see how much study product is absorbed by your body at all of your study visits. We will test these samples only in the event that you become infected with HIV.

- A pelvic examination twice a year. 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 exam. 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
    - The study staff may also collect samples from your cervix for a "Pap test". If the test shows a problem, it could mean you should have more tests. This will be performed at your Product Use End Visit.

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 (except at your Final Visit)
    - Contraception and ways to prevent getting pregnant (except at your Final Visit)
- Receive male condoms
- You will schedule your next visit (except at your Final Visit)

At any time during the study, the following may need to be collected if you are having symptoms or if clinicians suspect you may have an infection:

- Have vaginal and/or cervical swabs collected to test for infections
- Have a blood sample [Sites to insert amount] collected to test:
    - For infections passed through sex
    - For HIV
    - The health of your blood, liver and kidneys
- Have urine collected to test for:
    - Pregnancy
    - Infection

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

If you leave the study early, you will be asked to complete a final evaluation.

If you become infected with HIV
Your participation in this study will not cause HIV infection. However, there is always a chance that through sexual activity or other activities you may become HIV-positive. In the event you become HIV-positive, study staff will counsel and refer you for medical care and other available

services. You will continue to be counseled while you are in this study. You will have more tests to find out which drugs would be appropriate for your type of HIV-1 (HIV drug resistance). 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 may be referred to other research studies.

It may be necessary, depending upon local and national health requirements, for study staff to report diseases, including HIV, identified among 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. 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.

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
- Vulvovaginal or genital itching
- Abdominal discomfort
- Abdominal pain
- Urinary incontinence
- Nausea
- Vaginal or genital discharge

Other Possible Risks
It is possible that you may develop HIV drug resistance which means that drug resistant HIV will continue to replicate in the presence of the drug to which it has become resistant and using this

product could make it difficult to use dapivirine or drugs like it to treat HIV. Drug resistance only occurs if you were to become infected with HIV.

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/or your partner to try to help resolve them.

Some other studies of HIV prevention have found an unexpected higher risk of getting HIV among study participants. This could happen in any prevention study, including the MTN-020. Because of this, the study staff will remind you of the importance of using condoms to protect against HIV.

BENEFITS

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

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

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

Pregnancy

The ring with dapivirine and the placebo ring are not birth control. You must agree to use an effective method of birth control such as birth control pills or another hormonal-based method (except for vaginal rings), or an intrauterine device (IUD), unless you are sterilized.

We do not know what effect the study drugs have on pregnancy, including the effect of the study drug on the fetuses of women who use the vaginal ring when pregnant. Because of this, pregnant women may not join this study. 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 any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the ring may be causing bad effects, you will be told about this. It is important for you to know that other drugs are being tested for HIV prevention. HIV prevention researchers working on this study are committed to providing you with any data that becomes available, regardless of the product if it is found to be effective in preventing 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, Data Safety Monitoring Board (DSMB), 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 the 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

There are no gels, pills or vaginal rings currently available to protect against HIV during sex. **The only known way to protect against HIV during sex that is available is to use a condom every time you have sex.**

[*Sites to include/amend the following if applicable:* There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing and 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. 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 specify institutional policy:] It is unlikely that you will be injured as a result of study participation. This US federally funded study does not have the ability to provide compensation for research-related injury. If you are injured or become ill from taking part in this study, it is

important to tell your study doctor. Emergency treatment may be available but you or your insurance company will be charged for this treatment. You do not give up any legal rights by signing this consent form.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

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

PROBLEMS OR QUESTIONS

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

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

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 and cervical fluids 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 and cervical fluids for testing in future studies. You can still enroll in this study if you decide not to have blood, vaginal and cervical fluids stored for future studies. If you do not want the blood, vaginal and cervical fluids stored, we will destroy the 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

Members of the research team at this clinic may be able to visit you at your home or at another location as part of the study. Some of the scheduled study visits may take place at your home or other location outside of the research clinic, if you agree. 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 duration of it) and the procedures 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.

To conduct visits outside of the clinic we will need you to authorize us 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. 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.

_____ 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 have the study, please sign your name below.

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

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