

MTN-038

**A Phase 1, Randomized Pharmacokinetic and Safety Study of a 90 Day
Intravaginal Ring Containing Tenofovir**

Microbicide Trials Network

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MTN-038

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
AST	aspartate aminotransferase
AUC	area under the curve
b.i.d.	bis in die (twice daily)
BMI	body mass index
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
BV	bacterial vaginosis
CASI	computer assisted self-interview
CBC	complete blood count
CCR5	C-C chemokine receptor type 5
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
C _{max}	maximum concentration
CMRB	Clinical Microbicide Research Branch
CORE	Coordinating and Operations Center
CRF	case report form
CRMS	Clinical Research Management System
CROI	Conference on Retroviruses and Opportunistic Infections
CRS	clinical research site
C _{ss}	steady state concentration
CT	Chlamydia trachomatis, chlamydia
CTA	Clinical Trial Agreement
CVF	cervicovaginal fluid
CVL	cervicovaginal lavage
CWG	Community Working Group
CYP	cytochrome P450
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAPY	di-amino-pyrimidine
DLV	delavirdine
DMPA	depot medroxyprogesterone acetate
DNA	deoxyribonucleic acid
DPV	dapivirine
EAE	expedited adverse event
EC ₅₀	median effective concentration
EDC	electronic data capture
EFV	efavirenz
EMBRACE	Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure
ENR	Enrollment

FAME	Film Antiretroviral Microbicide Evaluation
FDA	(US) Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
FSH	follicle-stimulating hormone
FTC	emtricitabine
g	grams
GC	Neisseria gonorrhoeae, gonorrhea
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
hCG	human chorionic gonadotropin
HEC	hydroxyethylcellulose
HEENT	Head, Eye, Ear, Nose and Throat Examination
HHS	US Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HPV	human papillomavirus
hu-PBL	human peripheral blood lymphocytes
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	informed consent forms
ICH	International Council for Harmonisation
IDI	in-depth interview
IND	Investigational New Drug
IoR	Investigator of Record
IP	Investigational Product
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
IUD	intrauterine device
IVR	intravaginal ring
kg	kilogram
KOH	potassium hydroxide
LC	MTN Laboratory Center
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantification
LNG	levonorgestrel
LOC	MTN Leadership and Operations Center
µg	microgram
µM	micromole
m	meter
mg	milligram
MIV-160	(-)-cis-1-(5-Cyanopyridin-2-yl)-3-(4,7-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromen-1-yl)-urea, MSR-216; an NNRTI
mL	milliliter
mm	millimeter
MO	Medical Officer
MPID	Maternal and Pediatric Infectious Diseases
MTD	maximum tolerated dose
MTN	Microbicide Trials Network
NAAT	nucleic acid amplification test
ng	nanogram
NIAID	National Institute of Allergy and Infectious Diseases
NICHHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NL	network laboratory
nM	nanomole
NNRTI	non-nucleoside reverse transcriptase inhibitor

NOAEL	no-observed-adverse-effect-level
NVP	nevirapine
OHRP	Office for Human Research Protections
PD	pharmacodynamics
PEP	post-exposure prophylaxis
pg	picogram
PK	pharmacokinetics
PoR	Pharmacist of Record
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PSP	Prevention Sciences Program
PSRT	Protocol Safety Review Team
PTID	participant identification
PUEV	product use end visit
PVI	penile-vaginal intercourse
RE	Regulatory Entity
RNA	ribonucleic acid
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SCID	severe combined immunodeficiency
SCR	Screening
SDMC	Statistical Data Management Center
SHBG	sex hormone-binding globulin
SMC	Study Monitoring Committee
SMS	short message service
SOC	System Organ Class
SOP	standard operating procedure
SSP	study specific procedures
STI	sexually transmitted infection
SUSARs	suspected, unexpected serious adverse reactions
TDF	tenofovir diproxil fumarate
TEAE	treatment-emergent adverse events
TFV	tenofovir
Tmax	time to reach the maximum concentration
UA	urinalysis
UNAIDS	United Nations Programme on HIV/AIDS
UPMC	University of Pittsburgh Medical Center
USA	United States of America
USP	U.S. Pharmacopeial Convention
UTI	urinary tract infection
VIDD	Vaccine and Infectious Disease Division
VR	vaginal ring
WHO	World Health Organization
w/w	weight/weight

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MTN-038

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INVESTIGATOR SIGNATURE FORM

Version 1.0; July 11, 2018

A Study of the Microbicide Trials Network

Funded by:

Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
US National Institute of Mental Health
US National Institutes of Health (NIH)

IND Holder:

DAIDS (DAIDS Protocol ID: 38460)

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

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

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

Name of Investigator of Record (print)

Signature of Investigator of Record

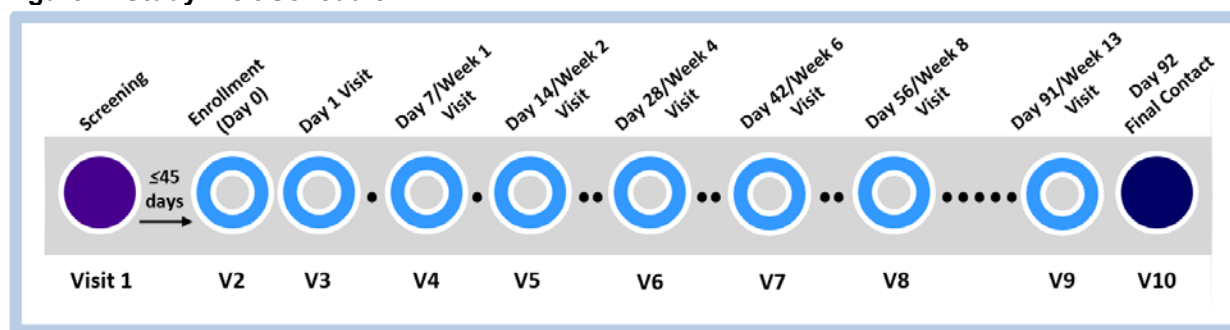
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Intravaginal Ring Containing Tenofovir

PROTOCOL SUMMARY

Short Title:	PK and Safety Study of a 90 Day Vaginal Ring Containing Tenofovir
Clinical Phase:	Phase 1
IND Sponsor:	DAIDS
Protocol Chair:	Albert Liu, MD, MPH
Sample Size:	Approximately 48 participants
Study Population:	Healthy, HIV-uninfected individuals assigned female sex at birth, 18-45 (inclusive) years old
Study Sites:	US site(s) selected by the MTN Executive Committee
Study Design:	Phase 1, two-arm, multi-site, randomized (2:1), placebo-controlled trial
Study Duration:	Approximately 92 days per participant, with approximately 6-9 months planned for accrual
Study Products:	Tenofovir (TFV) intravaginal ring (IVR) Placebo IVR
Study Regimen:	Participants will be randomized to the study products in a 2:1 TFV: placebo ratio and will not be told their group assignment. Participants will insert one IVR to be used for a period of approximately 91 days, followed by approximately 1 day of no product use

Figure 1: Study Visit Schedule



Primary Objectives:

Pharmacokinetics

- To characterize the local and systemic pharmacokinetics of one TFV IVR used continuously for 91 days

Safety

- To evaluate the safety of one TFV IVR used continuously for 91 days

Primary Endpoints:

Pharmacokinetics

- TFV levels in:
 - Plasma
 - Cervicovaginal fluid (CVF)
 - Rectal fluid
 - Cervical tissue
- Tenofovir diphosphate (TFV-DP) levels in:
 - Cervical tissue

Safety

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

Secondary Objectives:

Adherence

- To evaluate participant adherence to one TFV IVR used continuously for 91 days

Acceptability

- To evaluate the overall acceptability of one TFV IVR used continuously for 91 days

Secondary Endpoints:

Adherence

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

Acceptability

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

Exploratory Objectives:

Adherence

- To evaluate markers of ring use for the TFV IVR

Acceptability

- To evaluate components of acceptability of ring use for the TFV IVR

Vaginal Microenvironment

- To describe the genital microenvironment in HIV-uninfected participants during 91 days of continuous IVR use

Pharmacodynamics

- To determine the anti-HIV activity in CVF and cervical tissue
- To determine the anti-HSV-2 activity in CVF

Exploratory Endpoints:

Adherence

- Plasma and CVF TFV levels
- Residual drug levels in returned IVRs
- Biomarkers of ring use

Acceptability

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

Vaginal Microenvironment

- Changes in microbiota and biomarkers
- Impact of microbiota on TFV levels in tissue and plasma

Pharmacodynamics

- Measures of HIV inhibition in CVF and cervical tissue
- Measures of HSV-2 inhibition in CVF

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: A Phase 1, Randomized Pharmacokinetic and Safety Study of a 90 Day Intravaginal Ring Containing Tenofovir

Protocol Number: MTN-038

Short Title: PK and Safety Study of a 90 Day Vaginal Ring Containing Tenofovir

Date: July 11, 2018

1.2 Funding Agencies, 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
Rockville, MD 20852 USA

US National Institute of Mental Health (NIMH)
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Rockville, MD 20852 USA

US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
Maternal and Pediatric Infectious Diseases (MPID) Branch
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IND Sponsor: US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
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Monitor: Pharmaceutical Product Development, Inc. (PPD)
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1.3 Medical Officer

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1.4 Laboratory Centers

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1.5 Data Center

Data Center: MTN Statistical Data and Management Center (SDMC)
Statistical Center for HIV/AIDS Research & Prevention
(SCHARP)/Fred Hutchinson Cancer Research Center
(FHCRC)
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Qualitative Data Center: MTN Qualitative Data and Management Center (QDMC)
Women's Global Health Imperative program (WGHI)/
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1.6 Study Implementation

Study Implementation: MTN LOC - FHI 360
359 Blackwell Street, Suite 200
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2 INTRODUCTION

2.1 Microbicides in HIV/AIDS Prevention

In 2016, one million people lost their lives to human immunodeficiency virus (HIV)-related causes, and 1.8 million people around the world were newly infected.¹ Every 60 seconds, a young woman is infected with HIV.² Women and girls continue to be affected disproportionately by HIV in sub-Saharan Africa, where women account for approximately 60% of people living with HIV.³ The ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to women in under-resourced countries remains a public health priority.

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

With successful proof-of-concept that antiretroviral (ARV)-based microbicides reduce the risk of HIV-1 acquisition,^{4,5} confirmatory work and further trials involving different ARV compounds, various formulations, and different dosing strategies are required to provide options to end-users and to improve upon the level of product effectiveness.

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

Multiple clinical trials have evaluated the safety and effectiveness of tenofovir (TFV) for the prevention of HIV acquisition in vaginal gel⁶⁻⁹ and in oral tablet formulations.¹⁰⁻¹³ These clinical trials support the favorable safety profile and tolerability of TFV in general and specifically in vaginal and oral delivery formulations. Although the TFV vaginal gel formulation was not consistently shown to be effective for HIV prevention⁷⁻⁹, likely due to low rates of adherence, the efficacy of oral tablet formulations containing TFV is well-

established.¹⁰⁻¹³ However, high levels of adherence to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for pre-exposure prophylaxis (PrEP) are needed to protect against vaginal HIV acquisition. TFV delivered intravaginally may also help prevent herpes simplex virus type 2 (HSV-2) acquisition, as demonstrated in the CAPRISA 004 study of pericoitally applied TFV gel.¹⁴

The development of an extended duration intravaginal ring (IVR) may allow less frequent IVR replacements (e.g., quarterly basis instead of monthly basis) that may further reduce patient and provider burden, streamline follow-up, and improve adherence. Such a delivery mechanism could overcome the adherence and efficacy issues observed with the vaginal gel formulation of TFV and challenges with daily dosing of oral TDF/FTC, thus providing a viable vaginal delivery complement to the oral tablet.

MTN-038 is a collaboration between the Microbicide Trials Network (MTN) and CONRAD to evaluate the pharmacokinetics (PK) and safety of an extended duration (90 day) TFV IVR (loaded with 1.4 g TFV), as compared to a placebo ring.

2.2 Tenofovir

2.2.1 Description

TFV, 9-[(R)-2-(phosphonomethoxy) propyl]adenine or PMPA, is an adenosine nucleoside monophosphate analog of a nucleotide reverse transcriptase inhibitor (NtRTI) with potent activity against retroviruses. The orally bioavailable form of TFV, tenofovir disoproxil fumarate (TDF) (Viread®), has been approved for the treatment of HIV-1 infection since 2001 in the U.S. and since 2002 in Europe. TDF is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection and for the treatment of chronic hepatitis in adults. TDF is also a component of 3 marketed fixed-dose, orally administered combination products for treatment of HIV-1 infection: Truvada® (emtricitabine 200 mg/TDF 300 mg), Atripla (efavirenz 600 mg/emtricitabine 200 mg/TDF 300 mg), and Complera (emtricitabine 200 mg/TDF 300 mg/rilpivirine 25 mg). Gilead has approval from the U.S. Food and Drug Administration (FDA) for the use of Truvada for HIV prevention in both men and women.

PK studies of vaginally applied TFV have demonstrated lower blood levels and higher vaginal tissue levels of drug compared to oral administration, suggesting that topical administration may provide protection against vaginal acquisition of HIV with less systemic exposure to drug. Gilead has granted co-exclusive rights to CONRAD and the International Partnership for Microbicides (IPM) to develop and manufacture TFV as a microbicide gel and other dosage forms.

Evaluation of TFV formulated in a vaginal gel for prevention of HIV-1 has been conducted in multiple Phase I and II/IIb clinical studies. In a Phase IIb study of vaginally administered TFV 1% gel (CAPRISA 004), TFV was shown to significantly reduce HIV acquisition rates

by approximately 39% (CI 0.06 – 0.60, $p = 0.017$). In that study, the participants were instructed to insert one dose of gel up to 12 hours before sex and a second dose as soon as possible up to 12 hours after sex but no more than 2 doses in 24 hours, known as the BAT24 regimen.⁷ To confirm the CAPRISA 004 efficacy findings, an additional Phase III, multi-center, double-blind, randomized, placebo-controlled trial, the FACTS 001 study, was conducted to evaluate the safety and effectiveness of pericoital TFV 1% gel when using the BAT24 regimen. Unlike in the CAPRISA study, pericoital vaginal TFV 1% gel was not effective in preventing HIV acquisition in the FACTS 001 study; among 2029 sexually active, healthy women that were enrolled and included in the primary study analysis, 61 HIV infections occurred in the TFV arm and 62 in the placebo group (incidence rate ratio [IRR], 1.0; 95% CI: 0.7-1.4).⁹

Vaginal TFV 1% gel applied daily, as opposed to pericoitally, was also studied for HIV prevention in the VOICE study, a Phase IIb study designed and conducted by the MTN. The VOICE study (daily administration) did not confirm the protective benefit of TFV gel reported from the CAPRISA 004 study (pericoital dosing) due to low adherence: plasma levels of TFV were measurable in only 28% of participants in the oral TDF arm, 29% of women in the Truvada group, and 23% among those in the TFV gel group.⁸

TFV has been formulated as IVRs having a diameter of 55 mm and delivering 10 mg of TFV/day. This product is being evaluated in safety, PK, and pharmacodynamics (PD) studies to establish its usefulness as a vaginal microbicide product.

2.2.2 Mechanism of Action

TFV is an acyclic nucleotide analogue of adenosine monophosphate. TFV is an NtRTI. TFV requires subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate (TFV-DP). TFV-DP inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. TFV-DP is a weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ .

2.3 Nonclinical Studies of Tenofovir

A full battery of nonclinical studies has been carried out on oral TDF.¹⁵ In addition, nonclinical testing has been performed using TFV 1% gels.^{14,16} The toxicity of TFV has been studied in rats, rabbits, dogs, and monkeys. It has been administered intravenously, orally, subcutaneously, vaginally, and rectally. Except at very high systemic doses (i.e., ≥ 75 mg/kg), TFV is well tolerated. It is excreted primarily via the kidneys in unchanged form.

2.3.1 In vitro Studies of Tenofovir

In Vitro Pharmacology

Radiolabeled (^3H) TFV is rapidly taken up by resting (3-4 μM) and activated (1-2 μM) peripheral blood mononuclear cells (PBMCs), suggesting cellular uptake is via endocytosis. Once target cells have taken up TFV, subsequent metabolism appears to proceed quickly. The mono- and diphosphate metabolites of TFV accumulate rapidly, reaching approximately 1 μM and approximately 0.3 μM , respectively, at 6 hours post-exposure, whereas the adenine mono-phosphate (TFV) is not detectable to facilitate the formation of a barrier to HIV infection. This suggests that TFV is rapidly processed upon entry to the cell to TFV mono- and diphosphate, with a sufficiently long half-life to facilitate the formation and maintenance of a barrier to virus replication that could promote its deployment from both coitally associated and coitally disassociated microbicide applications.

Anti-HIV-1 Activity

The antiviral activity of TFV against laboratory and clinical isolates of HIV-1 has been assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood cells.¹⁷⁻¹⁹ The EC_{50} (50% effective concentration) values for TFV are in the range of 0.04 μM to 8.5 μM . TFV displays antiviral activity in cell cultures against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values range from 0.5 μM to 2.2 μM) and strain-specific activity against HIV-2 (EC_{50} values range from 1.6 μM to 5.5 μM).¹⁵

Resistance

Information regarding resistance studies can be found in the package inserts for Truvada¹⁰ and Viread.¹⁵

Condom Compatibility Studies of Tenofovir

The compatibility of TFV 1% vaginal gel (as well as matched placebo gel, and hydroxyethyl cellulose (HEC) placebo gel) with various types of male condoms were conducted.⁶ Studies included various male condoms: lubricated condoms, the Alatech Healthcare latex condoms, and other commercially available condoms such as Latex w/Silicone Lubricant by Rough Rider, Latex w/Aqueous Lubricant by Durex and Latex w/Aqueous Lubricant by Trojan, and many additional condom types.⁶

The airburst test was used to evaluate changes in film integrity (strength) and test specimens were measured before and after treatment with the gels to assess changes in dimensional profiles (shrinkage).

In general, the results show that there were no statistically significant changes in the strength properties following the application of the 3 gel preparations, or only slight changes but within the normal range. It was concluded that the TFV 1% gel, the matched placebo gel, and HEC placebo gel were all compatible with the condom types in this study. More details are provided in the TFV IVR investigator brochure (IB).⁶

2.3.2 In vivo (Animal Studies) of Tenofovir

Anti-HIV-1 Activity

Six studies conducted by the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) and two studies at the Centers for Disease Control and Prevention (CDC) were performed to test the hypothesis that vaginal dosing of TFV prevents vaginal transmission of virus. These studies provided proof-of-concept that TFV applied topically could prevent the transmission of simian immunodeficiency virus (SIV)/SHIV when vaginal dosing mimics coital usage and that extended protection may be possible. Although the total data are limited and a powered statistical determination as to the efficacy of TFV 1% gel versus 10% cannot be made, empirical examination of the efficacy data identifies TFV 1% gel as the lowest efficacious concentration tested when given within 2 hours of exposure. Thus, these data provided a scientific rationale for clinical study of vaginally applied TFV 1% gel as a method to prevent transmission of HIV. Two additional studies performed at the CDC using a repeat-challenge macaque model with a low-dose SHIV inoculum containing an R5-tropic HIV-1 envelope similar to naturally transmitted human viruses (10-50% tissue culture infective dose [TCID₅₀]) showed that application of TFV consistently protected from vaginal SHIV infection.⁶

Pharmacokinetics

Nonclinical PK testing has been carried out on oral TDF.¹⁵ In addition, nonclinical PK testing has been performed on TFV 1% vaginal gel.¹⁴ All nonclinical PK testing performed on the TFV IVR that is described in this section can be found in the TFV IVR IB.⁶

Rabbits: PK study of IVR segments

A PK and local tissue effects study of surgically implanted IVR segments containing TFV for 1, 2, and 3 months compared to once daily intravaginal administration of TFV 1% for 1 month was conducted in female rabbits (CONRAD Study 1645-066). TFV and placebo IVR segments loaded with approximately 0.23 g of the TFV/glycerin/water (equivalent to 0.15 g TFV per IVR segment, or approximately one-tenth the TFV loading of a full-sized IVR) or placebo were implanted in the abdominal (i.e., cranial) vagina.⁶

The mean TFV plasma PK parameters following dosing with TFV IVR segments or TFV gel in female rabbits for 28 days were the following: *TFV IVR segment*: T_{max} = 504 hours; C_{max} = 31.9 ng/mL; AUC_{0-t} = 14600 ng*hr/mL; AUC/Day (normalized per day for comparison) = 421 [ng*hr/mL]/Day. For the *TFV 1% gel*: T_{max} = 4 hours; C_{max} = 96.5

ng/mL; $AUC_{0-t} = 877$ (Day 1), 109 (day 15), 62.7 (Day 28) ng*hr/mL; AUC/Day (normalized per day for comparison) = 493 [ng*hr/mL]/Day. Mean (and standard deviation) TFV and TFV-DP concentrations in urinary vaginal tissues at 28 days post-TFV IVR segment implantation were 12,500 (9,260) ng/g and 404 (485) ng/g, respectively. Mean (and standard deviation) TFV and TFV-DP concentrations in urinary vaginal tissues after 28 days of daily intravaginal administration of TFV gel were 1870 (2610) ng/g and below limit of quantification, respectively. TFV and TFV-DP concentrations in urinary vaginal tissues were undetectable at 60 and 90 days post IVR implantation.

Measurable TFV concentrations were found in plasma of most animals treated with TFV IVR through day 45 and in vaginal tissue and fluids through day 29. Based upon evaluation of mean AUC/Day in animals with serial sample collections, systemic exposure to TFV was generally similar after intravaginal implantation of TFV ring segment (28 Days) and once-daily intravaginal administration of 10 mg/day TFV vaginal gel (28 Days).

Mean TFV concentrations in vaginal fluids were highest on Day 8 for animals implanted with a TFV IVR segment. By Day 45, levels dropped to BLQ and remained BLQ on days 61, 75, and 91. When comparing the first month of IVR segment implantation to daily intravaginal gel doses, the highest concentration evident with intravaginal gel doses was 3.2-fold higher than that of the ring segment group. In vaginal tissue, mean TFV and TFV-DP concentrations were higher for those animals implanted with a ring segment compared to those administered gel intravaginally. Mean TFV levels in tissue were 6.7- to 7.0-fold higher for animals implanted with a IVR segment. Measurable levels of mean TFV-DP were no longer detectable at 60 days post-implantation and, for mean free TFV, at 90 days post-implantation.⁶

Residual drug content analysis of TFV IVR segments retrieved from rabbits confirmed that $68.2 \pm 12.7\%$ of the total TFV load was released by day 29, giving time-averaged daily release rate of 3.7 ± 0.7 mg/d TFV. By day 61, >99.9% of the total TFV load had been released. It is unclear why the release rate in rabbits was observed to be higher than expected based on both in vitro drug release from IVRs (full-size IVRs or rabbit-size IVR segments) and sheep study results (below); however, differences in the geometry of the IVR segment compared to that of the full IVR may have played a contributing part.

Sheep

A GLP study, *Pharmacokinetic Study of Vaginal Ring or Gel Administration in Female Sheep (CONRAD 1645-071)*, evaluated the PK of TFV when administered as an IVR for up to 3 months or once daily vaginal gel administration for up to 28 days in female Dorset crossbred sheep. The IVR was administered once (on day 1) via vaginal insertion and remained in place for 90 days. The IVR contained approximately 1.6 g TFV for an intended daily dose of 10 mg/day, the same dose intended for use clinically. The vaginal gel was administered intravaginally once daily for 28 consecutive days. The vaginal gel contained 1% TFV in a 4 mL dose volume, giving a daily dose of approximately 40 mg/day. Blood and vaginal fluid samples were collected at various intervals to determine

TFV levels. In addition, vaginal tissue biopsy samples were collected (from the cranial and caudal vaginal sites) at various intervals and analyzed for TFV and TFV-DP. For the TFV gel group, PK samples were only collected after dosing on Days 1, 15 and 28. TFV IVRs were retrieved from the animals after 90 days of treatment and were analyzed for residual drug content. The residual drug content results were then used to estimate the in vivo daily release rate of TFV over the 90-day treatment period. At the termination of the study (day 31 for TFV gel group and day 94 for TFV IVR group), samples of vaginal tissue were taken and analyzed for free TFV and TFV-DP.

The mean TFV PK parameters following dosing with the TFV IVR and TFV 1% gel in female sheep are shown in Table 1. Mean TFV concentrations in plasma as functions of time post-TFV IVR insertion or time post-TFV 1% gel administration are shown in Figure 2. Mean TFV concentrations in caudal and cranial vaginal fluids are shown in Figure 3 for TFV IVRs and in Figure 4 for TFV 1% gel. Mean TFV concentrations in caudal and cranial vaginal tissues are shown in Figure 5 for TFV IVRs and in Figure 6 for TFV 1% gel.

Table 1: Mean (SD) TFV PK Parameters Determined following 90-day Intravaginal Treatment with TFV IVR and once-daily Intravaginal Administration of TFV 1% Gel for 28 Days in Sheep

	T_{\max} (h) ^a		C_{\max} (ng/mL or ng/g)		AUC_t (ng h/mL or ng h/g) ^b		AUC/d ([ng h/mL/d] or [ng h/g/d]) ^c	
	IVR (90 d)	Gel (28 d)	IVR (90 d)	Gel (28 d)	IVR (90 d)	Gel (28 d)	IVR (90 d)	Gel (28 d)
Plasma	336	2	31.3 (8.3)	46.8 (20.8)	32,052 (6,433)	n.a.	354 (71)	107 (66)
Vaginal Fluid (caudal)	72	8	5,092,569 (2,542,586)	898,257 (615,089)	2,427,074,548 (2,228,774,298)	n.a.	ND ^d	ND ^d
Vaginal Fluid (cranial)	504	336	23,646,483 (38,702,589)	1,119,417 (818,849)	13,434,760,463 (22,185,098,647)	n.a.	ND	ND
Vaginal Tissue (caudal)	2,160	8	88,088 (97,231)	8,134 (11,151)	49,837,599 (39,625,202)	n.a.	ND	ND
Vaginal Tissue (cranial)	1,056	8	45,288 (26,540)	27,491 (28,218)	51,625,202 (19,772,858)	n.a.	ND	ND

^a Median t_{\max} reported

^b AUC_t : Area under the curve from the time of dosing to the time of the last observation

^c Average AUC per Day for TFV IVR = $AUC_{0-2160}/90$

^d ND = Not determined

Figure 2: Mean (+SD) Plasma TFV Concentrations following Intravaginal Treatment with TFV IVRs (Left, $n = 8$) and TFV 1% Gel (Right, $n = 6-7$) in Female Sheep for 90 Days plus 3 Days following IVR Removal or 28 Days plus 3 Days following daily gel administration

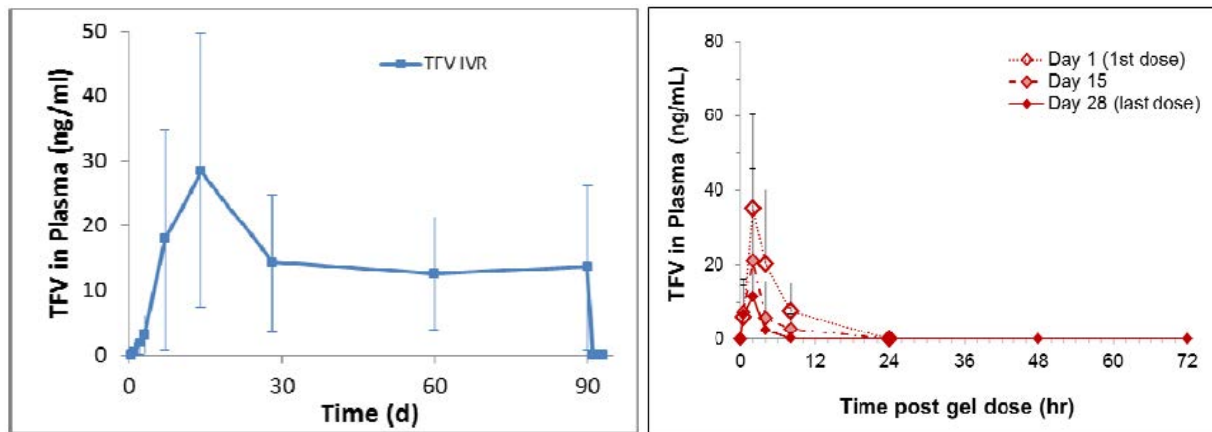


Figure 3: Mean (+SD) TFV Vaginal Fluid Concentrations following Intravaginal Treatment with TFV IVRs ($n = 8$) in Female Sheep for 90 days plus 3 days following IVR Removal

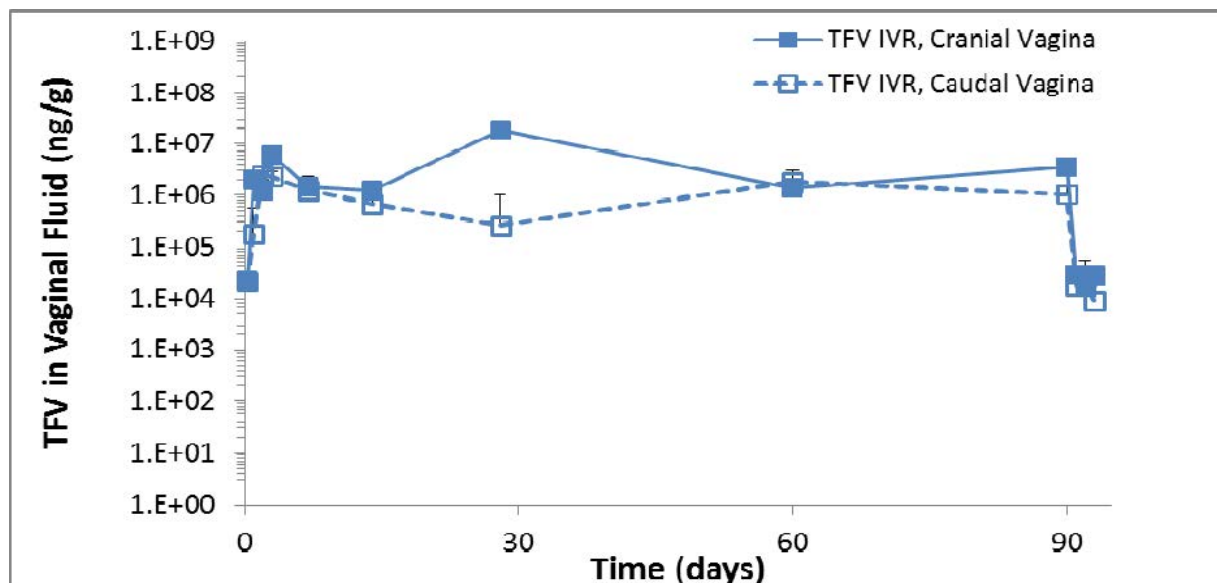


Figure 4: Mean (+SD) TFV Vaginal Fluid Concentrations following Intravaginal Treatment with TFV 1% Gel (n = 6-7) in Female Sheep for 28 days plus 3 days

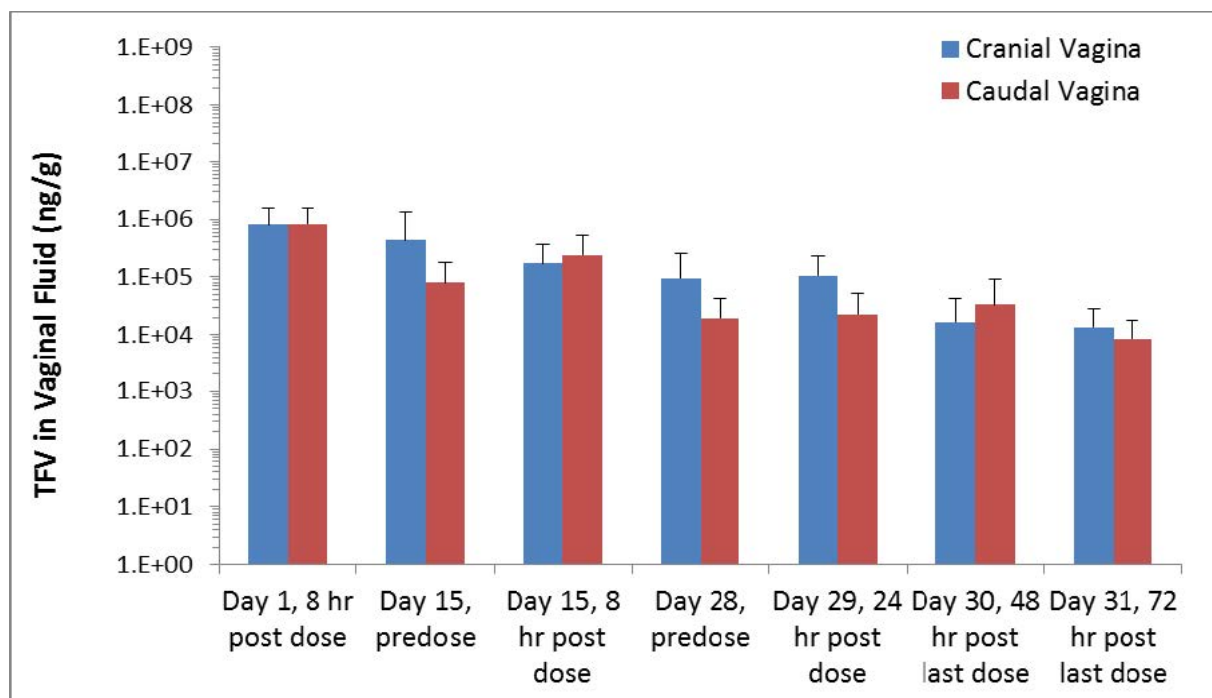


Figure 5: Mean (+SD) TFV Vaginal Tissue Concentrations following Intravaginal Treatment with TFV IVRs (n = 8) in Female Sheep for 90 days plus 3 days following IVR Removal

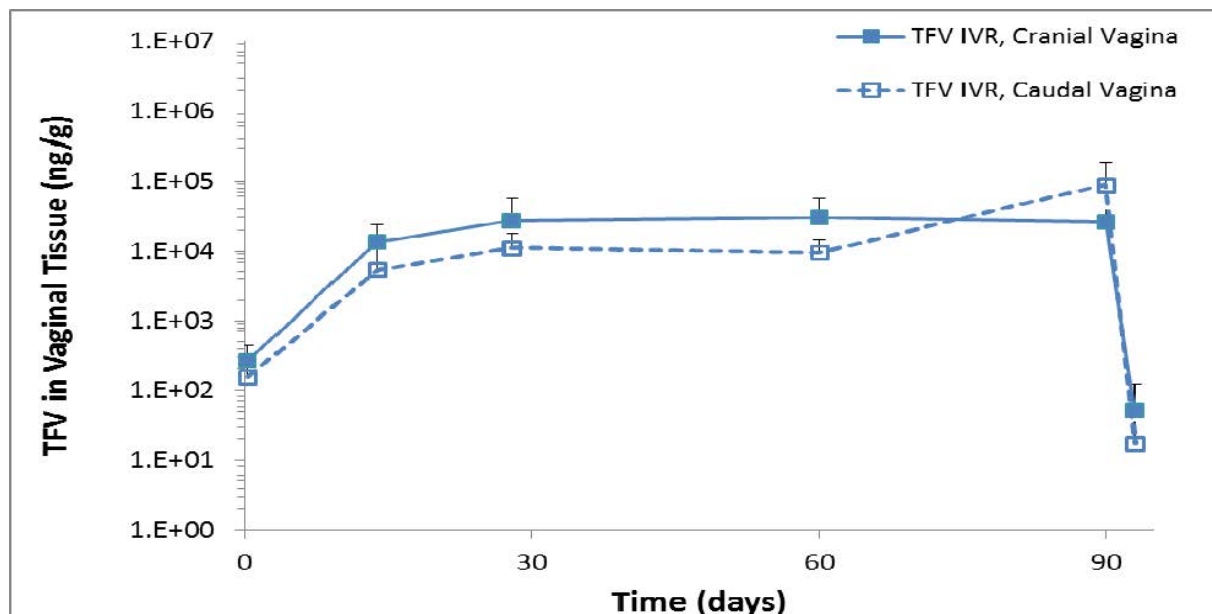
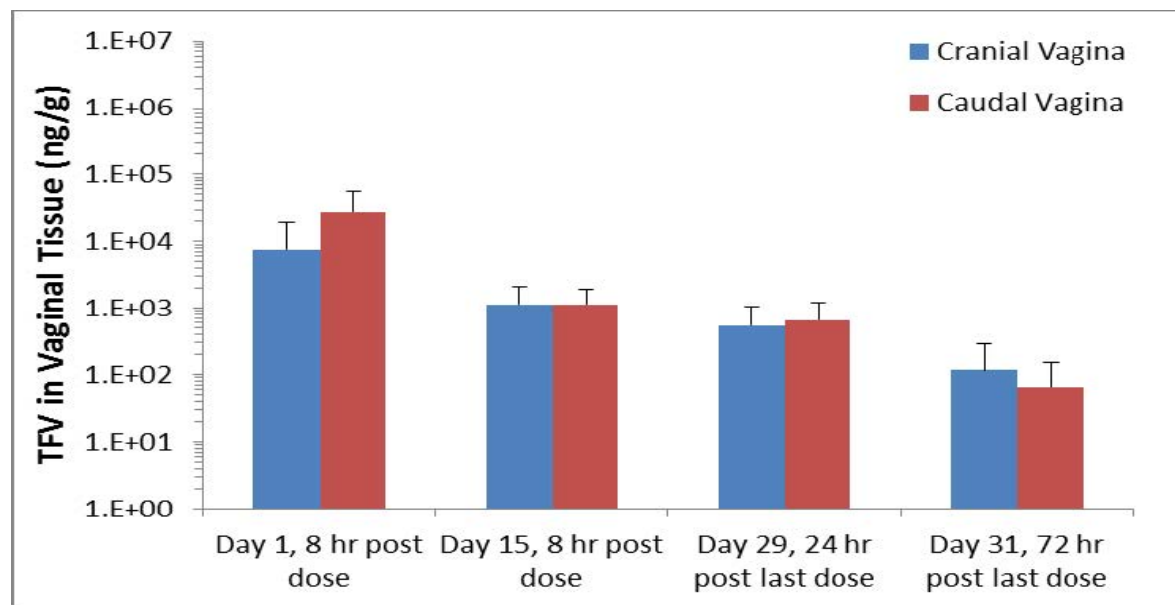


Figure 6: Mean (+SD) TFV Vaginal Tissue Concentrations following Intravaginal Treatment with TFV 1% Gel (n = 6-7) in Female Sheep for 28 days plus 3 days



Based upon comparison of mean C_{max} values, exposure to TFV in plasma was approximately 0.67-fold less following intravaginal implantation of TFV IVR than following once daily intravaginal administration of TFV 1% Gel. Based upon comparison of mean AUC/day, exposure to TFV in plasma was approximately 3.32-fold greater following intravaginal implantation of TFV IVR than following once daily intravaginal administration of TFV 1% Gel. In caudal and cranial vaginal fluids, mean C_{max} values were approximately 5.7- and 21.1-fold greater, respectively, following intravaginal implantation of TFV IVR than following once daily intravaginal administration of TFV 1% Gel. In caudal and cranial vaginal tissues, mean C_{max} values were approximately 10.8- and 1.7-fold greater following intravaginal implantation of TFV IVR than following once daily intravaginal administration of TFV 1% Gel. For vaginal fluids and vaginal tissue TFV AUC values, comparisons between the TFV IVR and TFV 1% Gel could not be made because the time points for PK evaluation were different. Therefore, comparisons between the two dosage forms were restricted to C_{max} .

Residual drug content analysis of TFV IVRs retrieved from sheep after 90 days of treatment revealed a time-averaged daily TFV release rate of 17.0 ± 1.1 mg/d.

TFV Reservoir Intravaginal Rings PK study in Macaques

This non-GLP study involved vaginal administration of miniature TFV IVRs to pigtail macaques (n=6) for 1 month for the assessment of PK and safety (*Study TPN1137-CON-2*). TFV plasma, and vaginal fluid were evaluated. Overall, TFV was detected at low (mean < 20 ng/mL) plasma levels and were sustained for the duration of treatment with the TFV IVR. Vaginal fluid levels were also sustained at mean levels of nearly 1×10^7 ng/g

(Weck-Cel spears collected proximal and distal to the IVR location) and 1×10^6 ng/mL (vaginal lavage). TFV levels in proximal and distal vaginal tissues were sustained at or above 1×10^5 ng/g, and TFV was detected in rectal tissues on the order of 1×10^1 to 1×10^3 ng/g. TFV-DP levels were BLQ in rectal tissues but were sustained at 170-1265 ng/g (~380-2830 fmol/mg) in vaginal tissues.

Residual drug content analysis was performed on retrieved TFV IVRs to estimate the time-averaged *in vivo* daily release rate. The time-averaged *in vivo* TFV release rate was 13.6 ± 7.6 mg/d. The *in vitro* release rate for these macaque-sized TFV IVRs was approximately 6.5 mg/d TFV. It is unclear why the mean *in vivo* release rate was higher in macaques; possible explanations may be IVR geometry or increased vaginal pH.

Toxicology (vaginal irritation studies)

Rabbit study (CONRAD Study 1645-066) involved assessment of the effect of TFV IVR segments surgically implanted into the vagina of rabbits for 1, 2, or 3 months as compared to intravaginal gel administration for one month (details provided in earlier section on PK). Both IVR and gel administration were well tolerated. No test article related effects were evident in the following parameters for either IVRs or gel: mortality, clinical observations, body weights, and macroscopic and microscopic pathology examinations.⁶

Macaque study (CONRAD Study PN1137-CON-2): Macaque-sized reservoir IVRs containing approximately 600 mg TFV or placebo were administered to female pigtailed macaques. The IVRs were kept in place for 28 days. Regular examination of the macaques throughout the study revealed no abnormal behavioral changes. Similarly, routine visual inspections of the vaginal compartment indicated that the TFV IVRs and placebo IVRs did not have any obvious detrimental effects on vaginal tissue. Menstrual cycle monitoring in the macaques by the analysis of plasma progesterone levels showed normal cycling during the study period. A comparative analysis of the levels of mucosal pro-inflammatory cytokines or chemokines between the two groups, as well as analysis of temporal-based cytokine/chemokine changes in individual macaques, showed minimal changes, if any, after IVR insertion.

2.4 Clinical Studies of Tenofovir

Oral preparations of TFV (as TDF, Viread) are currently marketed and the investigational TFV 1% vaginal gel has been studied in multiple clinical trials. In addition, two early phase clinical studies of the TFV IVR, CONRAD A13-128 and CONRAD A15-140, were recently conducted.

2.4.1 Safety and Pharmacokinetics of Orally Administered Tenofovir

Information regarding the safety and pharmacokinetics of orally administered tenofovir is available in the package inserts for Truvada¹⁰ and Viread.¹⁵

2.4.2 Safety and Pharmacokinetics of Vaginally Administered Tenofovir Gel

Safety of vaginally administered tenofovir gel

TFV 1% vaginal gel is generally very well tolerated with mostly mild, transient symptoms. Among women, most product-related AEs are genitourinary and most commonly include genital pruritus, genital burning, and vaginal discharge. Vaginal candidiasis was the most common infection, although its incidence varied between studies, occurring in between 2.1% of women (CONRAD A04-095) and 16% of women in HPTN 059, which is not surprising as the duration of use was 2 weeks compared to 24 weeks, respectively. The gel was also well tolerated in CONRAD A04-099, a male tolerance study of tenofovir gel following multiple topical exposures.¹⁴

In placebo-controlled trials [TFV-010, HPTN 059, CAPRISA 004, MTN-003 (VOICE), FACTS 001], there were generally no significant differences in adverse event (AE) rates between placebo and TFV gel arms.¹⁴ In the CAPRISA 004 study no increase in overall AE rates (including renal, hepatic, pregnancy-related, or genital AEs) was observed in the TFV 1% gel arm when compared to a placebo gel arm.⁷ In CAPRISA 004, the incidence of diarrhea was not statistically different between the arms, but when diarrhea was grouped with enteritis, diarrhea hemorrhagic, diarrhea infectious, dysentery, and gastroenteritis, the difference was significant (16.9% in TFV group vs. 11% in placebo group, $p=0.015$).⁶ VOICE was a large Phase 2B, randomized, placebo-controlled study that assessed the safety and effectiveness of daily oral TDF, oral TDF-FTC, or TFV 1% vaginal gel for the prevention of HIV infection in 5029 African women.⁸ In VOICE, no significant differences were observed in the frequencies of AEs between active and placebo arms, except for more frequent elevated serum creatinine levels among participants receiving oral TDF-FTC (1.3% vs. 0.2%, $p = 0.004$). FACTS 001 was a Phase 3, multi-center, double-blind, randomized, placebo-controlled trial conducted in South Africa to confirm the CAPRISA 004 findings.⁹ FACTS 001 evaluated the safety and effectiveness of pericoital TFV 1% gel when using the BAT-24 regimen, and also found no adverse safety signals for the TFV 1% gel when compared to placebo gel.

The incidence of colposcopic findings in one study (HPTN 050) was higher than that seen in the 14-day trial of the HEC universal placebo,²⁰ while the incidence in HPTN 059 was about the same. The clinical relevance of colposcopic findings has not been established.

Safety labs: Very few changes have been seen in tests evaluating renal function, liver function, and phosphate. Hypophosphatemia, which was mild and possibly product-related, was seen in 1 subject in HPTN 050.⁶

Microflora and vaginal immunity: In HPTN 059, the presence of *E. coli* and Enterococcus species increased significantly across all study arms from enrollment to week 24, and *Staphylococcus aureus* decreased ($p<0.05$). There were no significant differences between treatment vs. placebo arms or among regimens. No changes were seen in

inflammatory markers in 2 studies (HPTN 050 and HPTN 059). In TFV-010, several inflammatory markers (SLPI, IL-1 α , IL-1RA, and IL-8) were significant at a p-value of 0.05, but none were significant at a p-value of 0.01.⁶

Pharmacokinetics of vaginally administered tenofovir gel

Studies of vaginal administration of TFV gel uniformly show C_{max} values for TFV in the blood plasma of around 4 ng/ml, equal to approximately 1/100 the systemic concentration after oral dosing. Concentrations of TFV-DP in PBMCs were undetectable or very low.⁶ While the exact level of genital tract exposure needed to prevent HIV is not known, TFV concentrations in undiluted aspirated cervicovaginal fluid (CVF) of >1000 ng/ml were associated with protection from HIV in the CAPRISA 004 study.²¹ Median values for TFV C_{max} in CVF aspirate in the CONRAD A04-095 and MTN-001 studies were well above the protective level from the CAPRISA 004 study and were also well above the concentration seen after oral dosing.

The CONRAD A04-095 study indicated that both single and multiple dose exposures of TFV gel led to high genital tract levels up to 24 hours post-dose. Concentrations of TFV-DP, the active metabolite, were detectable in about 40% of the vaginal tissue biopsy samples at concentrations similar to or higher than what is seen in PBMCs after oral exposure.⁶ MTN-001 showed that TFV-DP levels in tissue after vaginal dosing are 100 times higher than after oral dosing. High concentrations of TFV-DP were also seen in endocervical cells.²²

Additional studies that reported vaginal TFV PK data in non-pregnant women include MTN-011 and MTN-014. MTN-011 was a Phase 1 study that evaluated the effect of sex on PK of vaginally administered TFV 1% gel. Compared with dosing without sex, median TFV concentrations after sex decreased 72% and 78% ($p < .001$) in CVF, 75% and 71% ($p < .001$) in vaginal tissue, and 75% ($p = .06$) and 55% ($p < .001$) in cervical tissue with -1 hour and -24 hour dosing, respectively. Median concentration of TFV-DP also decreased significantly in cervical tissue with -1 hour dosing. BAT dosing resulted in drug levels at least as great as those in the absence of sex.²³ MTN-014 was a Phase 1 cross-over study that evaluated the cross-compartment PK of TFV 1% gel (a reduced glycerin [RG] formulation) between the vagina and the rectum. After two weeks of daily administration of TFV 1% RG gel, TFV and TFV-DP levels were low or undetectable in cross-compartment tissue samples collected at 24 hours after administration of the last gel dose.²⁴

2.4.3 Safety and Pharmacokinetics of Tenofovir IVRs

To date, there have been two completed clinical studies to assess safety, PK, and PD of TFV in an IVR formulation: CONRAD A13-128 and CONRAD A15-140.

CONRAD A13-128 was a Phase 1, randomized, placebo-controlled, multi-site study to

assess the safety, PK, PD, and acceptability of the tenofovir and levonorgestrel intravaginal ring (TFV/LNG IVR) and the TFV-only IVR. Specifically, the study aimed to evaluate the safety of the TFV/LNG IVR, TFV-only IVR, and placebo IVR, PK of TFV and LNG, PD surrogates of contraceptive efficacy of LNG, and acceptability of all IVRs. The study enrolled healthy, non-pregnant, ovulatory, HIV-uninfected women aged 18 to 45 with a body mass index (BMI) less than 30 kg/m². Participants were assigned to use either the TFV-only IVR (release of 8-10 mg of TFV only per day), the TFV/LNG IVR (release of 8-10 mg of TFV and 20 µg of LNG per day), or the placebo IVR (no active experimental ingredients) for 16-18 days. Eighty-six participants were enrolled and 50 were randomized and completed the study across two sites, one in the United States and one in the Dominican Republic. The study was completed in February 2016.⁶

In the study, each participant had up to 9 study visits, depending on randomization. Following consent at Visit 1 and confirmation of eligibility, including confirmation of ovulation at Visits 1 and 2, participants underwent baseline sampling at Visit 3. Randomization and initiation of IVRs occurred at Visit 4. Fifty participants were randomized to type of IVR in a 2:2:1 ratio (20 TFV/LNG:20 TFV-only:10 placebo), as well as sampling time point at Visit 4 (1, 2, 4, or 8 hours post IVR insertion) and TFV PK biopsy collection time point post IVR removal (24 or 72 hours). Sample collection occurred 24 hours post IVR insertion (Visit 5), on the day of ovulation (Visit 6) based on an ovulation predictor kit, 8-10 days after ovulation (Visit 7), 24 hours post IVR removal (Visit 8), and 72 hours post IVR removal (Visit 9) based on randomization. Colposcopy was performed at Visit 4 (pre IVR insertion), 5, 6, and 7. In addition to sample collection, an acceptability questionnaire was completed at Visit 7. All participants received a follow up safety phone call 1-2 weeks following their last study visit.

The second study was CONRAD A15-140, a phase 1, prospective, parallel-group study designed to compare the anti-HIV efficacy of Truvada oral tablet and TFV intravaginal ring (IVR) at the cervicovaginal (CV) mucosal and fluid level using ex-vivo HIV infection models. The study enrolled healthy, non-pregnant, HIV-negative, premenopausal women (aged 18-50 years, with regular menstrual cycles) who were not at risk of pregnancy. Participants were assigned to use Truvada (combined FTC [200 mg] and TDF [300 mg] oral doses taken for 14 consecutive days) or TFV IVR (release of 8-10 mg TFV per day inserted vaginally and worn for 14 consecutive days). A total of 22 participants (12 in the Truvada group and 10 in the TFV IVR group) were enrolled and all of them finished the study. The study was completed in August 2016.⁶

During this study, participants completed 4 visits over a period of two to three months. At Visit 1 volunteers were consented and underwent procedures to confirm their eligibility for the study. Baseline blood for HIV, CBC, serum chemistries and Hepatitis B surface antigen (HBsAg) were collected, as well as genital swabs to test for Trichomonas, Gonorrhea and Chlamydia. At Visit 2 CVF, cervical and vaginal biopsies were collected. At Visit 3 a pelvic exam was conducted to ensure the site of biopsies had healed.

Participants were assigned the study product and instructed to use it for 14 days. When participants returned for Visit 4, product use data and follow-up blood, CVF and biopsy samples were collected. Final follow-up telephone calls were conducted approximately 1 to 2 weeks after Visit 4 to collect AEs experienced since the last visit. Participants then exited the study unless any symptoms required further follow up.

MTN-038 will be the first study to evaluate safety and PK of TFV IVR in humans for the full intended 90 days of use.

Safety of Tenofovir IVR

In CONRAD A13-128, there were no serious adverse events (SAEs). One participant in the TFV IVR group had two events considered possibly related to study product: a moderate headache lasting 2 days and mild vulvovaginal pruritus lasting 3 days, both of which resolved without sequelae. There were no product-related events nor AEs leading to discontinuation of IVR use. The only IVR discontinuation during the study was due to personal reasons and not related to study product or procedures. Only one event met the definition for moderate or severe urogenital AE in a woman in the TFV IVR group: an episode of severe vulvovaginal pain considered related to a study procedure but not study product, which resolved without sequelae after 10 hours. There were 6 unrelated TEAEs in 4 women in the placebo arm: 3 nasopharyngitis, 1 abdominal pain, 1 procedural pain, and 1 triglyceride change. No significant colposcopic findings or abnormalities in vital signs or physical exam were noted in participants.⁶

In CONRAD A15-140, ten participants were enrolled in the TFV IVR group. Overall, the TFV IVR inserted vaginally and worn for 14 consecutive days appeared to be generally safe and well-tolerated in this population. Overall, 2 participants out of 10 reported 2 TEAEs, bladder discomfort and a procedural complication. There were no clinically important changes noted in clinical laboratory evaluations, vital signs, physical examinations, or pelvic examinations with respect to safety.

A Phase 1, randomized, single-blind, placebo-controlled trial was conducted to evaluate the safety and pharmacokinetics of 3 months use of a tenofovir disoproxil fumarate (TDF) IVR (360 mg + 60 mg NaCl) in sexually active women on contraception (at least 4 sex acts per month). Participants were assigned in a 3:1 ratio to TDF IVR or placebo. In total, 17 of 40 planned women were enrolled before study termination (12 TDF, 5 placebo). The study was terminated early because 8 participants in the TDF arm developed Grade 1 vaginal and cervical ulceration, which occurred on average 32 days after ring use (range 23-56 days). Two women in the TDF arm completed the study without any complications and the study team elected to remove the ring early in 2 others. Four of 8 women with ulceration were symptomatic and 3 had bilateral ulcers. All ulceration resolved after ring removal. No ulcers developed with the placebo IVR. A total of 70 AEs was reported for the study, 66 of them were Grade 1 and 4 were Grade 2. No Grade 3 or 4 AEs or SAEs were reported.²⁵

Pharmacokinetics of Tenofovir IVR

In CONRAD A13-128, all participants had plasma TFV levels below the limit of quantification (BLQ) at baseline. The plasma TFV levels rose to a median (IQR) of 2.3 (1.7-3.3) ng/mL prior to IVR removal, which is well within the low range expected from topical dosing of TFV vaginal gel as compared to oral dosing of TFV, and fell to BLQ values within 24 hours of IVR removal. These data support that after 16-18 days of IVR use, plasma TFV levels remain in the low range expected for topical dosing. TFV concentrations in CV aspirate exceeded 1,000,000 ng/mL (n=38) during IVR use and 1,000 ng/mL at 24 hours post removal, suggesting that the IVR delivers consistent TFV concentrations similar to or exceeding peak concentrations achieved with TFV 1% gel. TFV and TFV-DP concentrations in vaginal tissues during IVR use and post IVR removal were also consistent with ranges found after dosing of TFV vaginal gel in women.⁶

In CONRAD A15-140, concentrations of TFV in plasma were greater following oral treatment with Truvada than following TFV IVR, while concentrations of TFV and TFV-DP in cervical and vaginal tissue were greater following TFV IVR use than following Truvada. TFV and TFV-DP concentrations met established concentrations in tissue after 14 days of IVR use. TFV concentrations in the plasma was low as expected with topical administration. Median TFV concentrations in tissue were $>10^4$ ng/g and median TFV-DP concentrations in tissue were $>10^6$ fmol/g.

Pharmacodynamics of Tenofovir IVR

In CONRAD A13-128, once participants were exposed to TFV-containing IVRs, the HIV inhibitory activity of the CV secretions increased to the range of 99% inhibition, similar to levels seen with use of TFV vaginal gel. The mean production of HIV p24 antigen in tissue was lower in the presence of TFV, and the lack of increased production of p24 throughout the culture period (21 days) in tissues exposed to TFV suggests inhibition of HIV replication.⁶

In CONRAD A15-140, anti-HIV activity of CVF was measured in TZM-bl cells infected with HIV-1BaL. There were statistically significant decreases from baseline in cervical fluid mean infection percentage after TFV IVR use for 14 days.

2.4.4 Efficacy of Tenofovir (for HIV prevention in women)

Orally administered tenofovir

Information regarding the efficacy of orally administered TFV for HIV prevention in women (and in men having sex with men) is available in the package inserts for Truvada¹⁰ and Viread.¹⁵

Vaginally administered tenofovir (Gel Studies)

CAPRISA 004 was a large Phase 2B, randomized, double-blind, placebo-controlled study that assessed the safety and effectiveness of vaginal TFV 1% gel for the prevention of HIV infection in South African women. CAPRISA 004 results indicated that coitally related TFV gel use (using the BAT-24 regimen) reduced HIV infection in women by an estimated 39%. This protective effect was evident irrespective of sexual behavior, condom use, HSV-2 infection, or urban/rural differences. A trend of higher effectiveness was observed as gel adherence improved: high adherers in the tenofovir gel arm had a 54% lower HIV incidence rate.⁷

MTN-003 (VOICE) was a large Phase 2B, randomized, placebo-controlled study that assessed the safety and effectiveness of daily treatment with oral TDF, oral TDF-FTC, or TFV 1% vaginal gel for the prevention of HIV infection in 5029 African women.⁸ Results of VOICE showed that neither oral TDF, oral TDF-FTC nor TFV gel were effective in reducing HIV acquisition. The main reason was low adherence across all groups, with only 25-30% of women having used the study product.⁸

FACTS 001 was a Phase 3, multi-center, double-blind, randomized, placebo-controlled trial conducted in South Africa to confirm the CAPRISA 004 findings. FACTS 001 evaluated the safety and effectiveness of pericoital TFV 1% gel when using the BAT-24 regimen. However, pericoital vaginal TFV 1% gel failed to confirm the results of CAPRISA 004. The gel was not effective in preventing HIV acquisition. Among the 2029 sexually active, healthy women that were enrolled and included in the primary analysis, 61 HIV infections occurred in the TFV arm and 62 in the placebo group (incidence rate ratio [IRR], 1.0; 95% CI: 0.7-1.4). However, TFV gel was effective only in women who reported consistent product use.⁹

2.5 Study Hypotheses and Rationale for Study Design

2.5.1 Study Design

The design of MTN-038, a clinical study of the TFV IVR, will provide data to compare the PK and safety profile of an extended duration TFV IVR (1.4 g) to a placebo IVR. A single IVR will be used continuously for approximately 91 days (13 weeks); this period of time was selected to optimize scheduling feasibility at study sites. (Note that the 92-day study duration takes the final visit into account.) *In vitro* release testing performed by CONRAD during IVR formulation development demonstrated that IVRs like the one being evaluated in this study provided high sustained release and high levels of TFV over a 90-day period.⁶ It is important to note that the drug exposure due to the release from 90-day TFV IVR is anticipated to fall within pre-established preclinical and clinical safety margins for which vaginally administered data exist.⁶

MTN-038 will evaluate TFV and TFV-DP levels in plasma, CVF, rectal fluid, and cervical tissue during approximately 91 days of continuous use of a single ring containing 1.4 g

TFV. PK data will help determine the concentration-time profile using pooled data across all participants. The study design includes frequent collection of corresponding blood, rectal and CVF samples following the insertion of a TFV IVR to allow for the detection of drug release from the ring. PK parameters of TFV will be calculated for blood plasma, CVF, rectal fluid, and cervical tissue.

2.5.2 Study Hypotheses

- Plasma, CVF, and rectal fluid TFV levels and cervical tissue TFV and TFV-DP levels will be measurable in all participants
- Continuous exposure to TFV due to sustained release from the 1.4 g TFV IVR for 91 days will be safe

3 OBJECTIVES

3.1 Primary Objectives

Pharmacokinetics

- To characterize the local and systemic pharmacokinetics of one TFV IVR used continuously for 91 days

Safety

- To evaluate the safety of one TFV IVR used continuously for 91 days

3.2 Secondary Objectives

Adherence

- To evaluate participant adherence to one TFV IVR used continuously for 91 days

Acceptability

- To evaluate the overall acceptability of one TFV IVR used continuously for 91 days

3.3 Exploratory Objectives

Adherence

- To evaluate markers of ring use for the TFV IVR

Acceptability

- To evaluate components of acceptability of ring use for the TFV IVR

Vaginal Microenvironment

- To describe the genital microenvironment in HIV-uninfected participants during 91 days of continuous IVR use

Pharmacodynamics

- To determine the anti-HIV activity in CVF and cervical tissue
- To determine the anti-HSV-2 activity in CVF

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-038 is a Phase 1, two-arm, multi-site, randomized (2:1), placebo-controlled trial of a polyurethane reservoir IVR containing the active ingredient TFV. Participants will not be told their group assignment to minimize potential bias in self-reports. The 1.4 g study IVR is inserted once and used continuously for a total of approximately 91 days by healthy, HIV-uninfected participants age 18-45 (inclusive).

4.2 Primary Endpoints

Pharmacokinetics

- TFV levels in:
 - Plasma
 - Cervicovaginal fluid (CVF)
 - Rectal fluid
 - Cervical tissue
- Tenofovir diphosphate (TFV-DP) levels in:
 - Cervical tissue

Safety

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

4.3 Secondary Endpoints

Adherence

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

Acceptability

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

4.4 Exploratory Endpoints**Adherence**

- Plasma and CVF TFV levels
- Residual drug levels in returned IVRs
- Biomarkers of ring use

Acceptability

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

Vaginal Microenvironment

- Changes in microbiota and biomarkers
- Impact of microbiota on TFV levels in tissue and plasma

Pharmacodynamics

- Measures of HIV inhibition in CVF and cervical tissue
- Measures of HSV-2 inhibition in CVF

4.5 Description of Study Population

The study population will be healthy, HIV-uninfected participants, 18-45 (inclusive) who meet the criteria outlined in [Section 5.2](#) and [Section 5.3](#).

4.6 Time to Complete Accrual

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

4.7 Study Groups

Approximately 48 participants will be randomized in a 2:1 ratio to either 1.4 g TFFV IVR or to a placebo IVR.

4.8 Expected Duration of Participation

The expected trial duration for each enrolled participant is approximately 92 days.

4.9 Sites

Sites selected by the MTN Executive Committee.

5 STUDY POPULATION

5.1 Selection of the Study Population

The inclusion and exclusion criteria in [Section 5.2](#) and [Section 5.3](#) will be utilized to ensure the appropriate selection of study participants.

5.1.1 Recruitment

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

5.1.2 Retention

Once a participant is enrolled/randomized in MTN-038, the study site will make every effort to retain the participants in follow-up to minimize possible bias associated with loss-to-follow-up. An average retention rate of 95% will be targeted at each site. All study sites will be responsible for developing and implementing local standard operating procedure (SOPs) to achieve this. Engaging peer educators/advocates or organizations in retention messaging, etc. may be used to facilitate MTN-038 retention.

5.2 Inclusion Criteria

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

- 1) Assigned female sex at birth

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

- 2) Age 18 through 45 years (inclusive) at Screening, verified per site SOPs
- 3) Able and willing to provide written informed consent to be screened for and enrolled in MTN-038
- 4) Able and willing to provide adequate locator information, as defined in site SOPs
- 5) Able to communicate in spoken and written English
- 6) Available for all visits and able and willing to comply with all study procedural requirements
- 7) Willing to abstain from receptive vaginal or anal sexual activities for 72 hours prior to each clinical visit and for 72 hours after biopsy collection
- 8) Willing to use male condoms for penile-vaginal and penile-rectal sexual intercourse for the duration of study participation
- 9) Per participant report, using an effective method of contraception for at least 30 days (inclusive) prior to Enrollment, and intending to continue use of an effective method for the duration of study participation; effective methods include:
 - hormonal methods (except contraceptive vaginal ring)
 - intrauterine device (IUD)
 - sterilization (of participant or partner, as defined in site SOPs)
 - having sex exclusively with individuals assigned female sex at birth
 - sexually abstinent as defined by abstaining from penile-vaginal intercourse for 90 days prior to Enrollment, and intending to remain abstinent for the duration of study participation
- 10) In general good health as determined by the Investigator of Record (IoR)/designee at Screening and Enrollment
- 11) HIV-uninfected based on testing performed at Screening and Enrollment (per protocol algorithm in [Appendix II](#))

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

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

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

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

- 14) Participants over the age of 21 (inclusive) must have documentation of a satisfactory Pap within the past 3 years prior to Enrollment consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 (Dated November 2007) to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, or satisfactory evaluation with no treatment required of Grade 1 or higher Pap result
- 15) At Screening and Enrollment, agrees not to participate in other research studies involving drugs, medical devices, vaginal or rectal products, or vaccines after the Screening Visit and for the duration of study participation

5.3 Exclusion Criteria

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

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

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

- 2) Diagnosed with symptomatic urinary tract infection (UTI) or reproductive tract infection (RTI) at Screening or Enrollment

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

Note: Asymptomatic BV and candidiasis are not exclusionary.

- 3) Diagnosed with an acute sexually transmitted infection (STI) requiring treatment per current Centers for Disease Control and Prevention (CDC) guidelines (<http://www.cdc.gov/std/treatment/>) at Screening or Enrollment such as gonorrhea, chlamydia, trichomonas, pelvic inflammatory disease, and/or syphilis

Note: Genital warts requiring treatment and frequent recurrence of HSV are considered exclusionary; however, infrequent HSV outbreaks are not. Genital warts requiring treatment are defined as those that cause undue burden or discomfort to the participant, including bulky size, unacceptable appearance, or physical discomfort. See MTN-038 Study-Specific Procedures (SSP) Manual for additional information.

- 4) Has a clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff) at Screening or Enrollment. *

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

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

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

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

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

- f) Currently breastfeeding or planning to breastfeed during the study
 - g) Participation in any other research study involving drugs, medical devices, vaginal or rectal products, or vaccines, in the 60 days prior to Enrollment
- 6) Use of pre-exposure prophylaxis (PrEP) for HIV prevention and/or post-exposure prophylaxis (PEP) for potential HIV exposure within the 3 months prior to Enrollment, and/or anticipated use and/or unwillingness to abstain from PrEP during trial participation

- 7) Has any of the following laboratory abnormalities at Screening Visit:
- a) Grade 1 or higher Aspartate aminotransferase (AST) or alanine transaminase (ALT)*
 - b) Grade 1 or higher Hemoglobin*
 - c) Calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula
 - d) Positive Hepatitis B surface antigen result

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

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

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

5.4 Co-enrollment Guidelines

As indicated in [Section 5.2](#) and [Section 5.3](#), participants must not take part in other research studies involving drugs, medical devices, vaginal or rectal products, or vaccines after the Screening Visit and while taking part in MTN-038 unless approved by the Protocol Safety Review Team (PSRT) and Protocol Chair. Participation in the following types of studies may be allowed at the discretion of the IoR/designee after consultation with the Protocol Chair and PSRT:

- Participants may take part in MTN ancillary studies
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-positive persons
- Participants who become pregnant while on study product will be offered enrollment in MTN-016 (provided their study site is taking part in MTN-016)

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-038, the IoR/designee will consult the PSRT regarding ongoing product use and other potential safety considerations associated with co-enrollment.

6 STUDY PRODUCT

6.1 Regimen

Each participant will be randomized to one of two IVRs:

Table 2: Study Regimen

Group	N	Ring Description
A	32	TFV IVR containing 1.4 g TFV
B	16	Matching Placebo IVR

Each participant will receive either an TFV IVR containing 1.4 g TFV or a matching placebo IVR. Participants will be randomized in a 2:1 ratio. Participants will not be told their group assignment. The IVR is inserted once and used continuously for approximately 91 days. The IVR will be removed by the participant (or clinician/designee, if necessary) at the product use end visit (PUEV/Early Termination Visit). Participants will be followed for approximately 1 day following final IVR removal.

6.2 Administration

At the Enrollment Visit the IVR will be inserted by the participant (or clinician/designee, if necessary). Participants will be given detailed instructions in the clinic on proper IVR insertion and removal procedures. Details on administration (ring insertion, removal, procedures in the event of expulsion) will be provided in the MTN-038 Study-Specific Procedures (SSP) Manual.

6.3 Study Product Formulation and Storage

The 1.4 g TFV IVRs are designed to provide sustained release of drug for a 90-day period.

6.3.1 1.4 g TFV IVR

The 1.4 g TFV IVR is comprised of a drug-loaded hydrophilic polyether urethane (HPU) tube (white segment) that is sealed and joined together (transparent joint) to form the shape of a ring. This is a reservoir IVR using a water-absorbable polyurethane as a rate controlling membrane capable of delivering approximately 10 mg/day TFV for 90 days. The TFV IVR has a 0.7 mm wall thickness, 5.5 mm outer cross-sectional diameter and 55 mm outer diameter.

The TFV IVRs should be stored in the site pharmacy at 20°C to 25°C (68°F to 77°F), with allowable excursions between 15°C to 30°C (59°F to 86°F).

6.3.2 Matching Placebo IVR

The matching Placebo IVR has a similar appearance and dimensions to the TFV IVR. The composition of the matching Placebo IVR is also similar to the TFV IVR except that modified starch, which is non-eluting from the reservoir, is used to replace the TFV to provide a similar white filled tube appearance.

The matching Placebo IVRs should be stored in the site pharmacy at 20°C to 25°C (68°F to 77°F), with allowable excursions between 15°C to 30°C (59°F to 86°F).

6.4 Supply and Accountability

6.4.1 Supply

CONRAD (Arlington, VA) will oversee the manufacture of all the study IVRs and analysis/release of the rings under Good Manufacturing Practices (GMP). The API TFV is supplied by Gilead Sciences, Inc.

6.4.2 IVR Dispensing

Study IVRs will be dispensed from the pharmacy to clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. Participants will receive one TFV or placebo IVR at the enrollment visit (Visit 2) and will use the IVR for approximately 91 days. Provisions for the dispensation of additional IVRs will be at the discretion of the IoR and in consultation with the PSRT as needed.

6.4.3 Accountability

Each Clinical Research Site (CRS) Pharmacist of Record (PoR) is required to maintain a complete record of all IVRs received and subsequently dispensed. All unused study products must be returned to the MTN Pharmacist after the study is completed or terminated unless otherwise instructed by the MTN Pharmacist. The procedures to be followed are provided in the MTN-038 Pharmacy Study Product Management Procedures Manual.

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

6.4.4 Retrieval of Used Study Product

Study participants will be instructed to return for IVR removal at the PUEV/Early Termination Visit. If the participant has removed the IVR and it is not returned at the PUEV/Early Termination Visit, site staff members will make every effort to encourage

participants to return the IVR as soon as possible (optimally within 5 working days). Attempts by study staff to retrieve the IVR from the participant must be documented.

When product use is permanently discontinued for HIV infection or pregnancy, the IVR must be retrieved (optimally within 24 hours of site awareness) and returned to the clinic (see Table 3 below). Additional IVR retrieval specifications in response to discontinuations for other reasons, or IoR discretion, can be found in Table 3. Study product retrieval may occur either by the participant returning the IVR to study staff within the specified timeframe or attempts should be made by study staff to contact the participant and retrieve the IVR as soon as possible. If the IVR is not returned within the time frames outlined below, the MTN-038 PSRT must be notified.

Table 3: Retrieval of IVR

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

If there is a product hold, expulsion (i.e., ring removed and cannot be reinserted) or an extended period of time that the ring is removed, the MTN-038 PSRT should be notified. The PSRT will evaluate each reported event to determine if the ring should be reinserted, if a new ring should be dispensed, or if the participant should discontinue product use. See [Section 9](#) for additional information related to product holds. Additional guidance regarding ring expulsions and/or removals will be provided in the SSP.

6.5 Concomitant Medications

Enrolled study participants may use concomitant medications during study participation with the exception of medications and products noted as prohibited in [Sections 6.6](#) and [6.7](#). All concomitant medication use reported throughout the course of the study, including all prescription medications, over-the-counter preparations, vitamins, nutritional supplements, and herbal preparations, will be entered on case report forms (CRFs) designated for that purpose.

6.6 Prohibited Medications

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

Participants are asked to abstain from using aspirin (greater than 81 mg) within 72 hours prior to and following a cervical biopsy collection visit (Visits 5 and 8 or Visits 6 and 9). Should a participant report taking any of the medications noted above which may increase risk of bleeding or engaging in receptive vaginal or anal sexual activities the visit should be rescheduled within the visit window, if possible. If it is determined that rescheduling the visit within the window is not possible, the visit may proceed at IoR discretion after proper participant counseling has occurred.

6.7 Intravaginal and Rectal Medications, Products and Practices

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

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

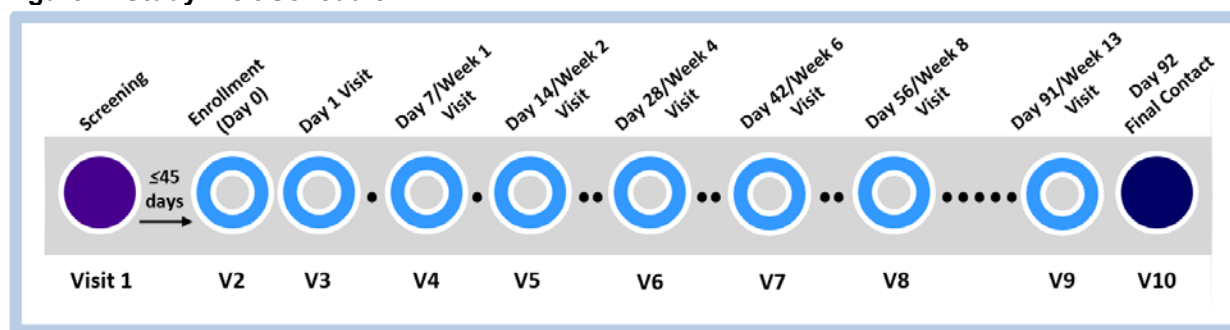
While tampon use is not prohibited, participants will be instructed to restrict use for 24 hours prior to any clinic visit in which CVP samples are collected.

Participants will be offered male condoms if indicated and/or per local standard of care. The condoms will be made available in the clinic and will be dispensed by the clinic staff.

7 STUDY PROCEDURES

An overview of the study visit and evaluation schedule is provided in [Appendix I](#). Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites as well as to specify the visit windows are provided in the MTN-038 SSP Manual available at www.mtnstopshiv.org.

Figure 7: Study Visit Schedule



7.1 Pre-screening

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

7.2 Screening Visit - Visit 1

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

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

Table 4: Screening Visit - Visit 1

Screening Visit - Visit 1		
Component		Procedure/Analysis
Administrative and Regulatory		<ul style="list-style-type: none"> Obtain written informed consent Assign a unique Participant Identification (PTID) number Assess eligibility Collect demographic and background information Collect locator information Provide reimbursement Schedule next visit/contact*
Behavioral/Counseling		<ul style="list-style-type: none"> HIV pre- and post-test counseling HIV/STI risk reduction counseling Protocol counseling
Clinical		<ul style="list-style-type: none"> Collect medical eligibility information (including exclusionary medical conditions and medications) Collect medical and menstrual history Collect concomitant medications Perform physical examination Perform pelvic examination Treat or prescribe treatment for RTI/UTI/STIs* Provide available test results
Laboratory	Urine	<ul style="list-style-type: none"> Pregnancy test π Urine dipstick/culture*
	Blood	<ul style="list-style-type: none"> HIV-1/2 testing Complete blood count (CBC) with differential and platelets Serum creatinine AST/ALT Hepatitis B surface antigen Syphilis serology
	Pelvic Samples	<ul style="list-style-type: none"> Nucleic acid amplification test (NAAT) for GC/CT and trichomonas Pap test[^] Saline/potassium hydroxide (KOH) wet mount with pH for candidiasis and/or bacterial vaginosis (BV)*
Study Product Supply		<ul style="list-style-type: none"> Offer male condoms*

* If indicated and/or per local standard of care

[^] If indicated (if participant [over age 21] is unable to provide documentation of a satisfactory Pap test within 3 years prior to enrollment)

π Not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records

7.3 Enrollment Visit - Visit 2 (Day 0)

All enrollment procedures must occur on the same day. The participant's menstrual cycle must be considered when scheduling Visit 2-Enrollment (Day 0). Ideally, no bleeding should occur within the first 7 days of product use, e.g., Study Visits 2-4 (Days 0, 1, and

7). Participants will be randomized to provide cervical tissue samples at either Visits 5 and 8 (Days 14 and 56) or at Visits 6 and 9 (Days 28 and 91).

Table 5: Enrollment Visit - Visit 2 (Day 0)

Enrollment Visit - Visit 2 (Day 0)		
Component		Procedure/Analysis
Administrative and Regulatory		<ul style="list-style-type: none"> • Assess and confirm eligibility • Review/update locator information • Randomization to product and biopsy schedule • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling		<ul style="list-style-type: none"> • HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Protocol counseling • Collect product preference/acceptability information • Behavioral assessment
Clinical		<ul style="list-style-type: none"> • Collect medical eligibility information (including exclusionary medical conditions and medications) • Review/update medical and menstrual history • Review/update concomitant medications • Perform targeted physical examination • Perform pelvic examination • Treat or prescribe treatment for RTI/UTI/STIs* • Digital examination by clinician to check IVR placement • Provide available test results
Laboratory	Urine	<ul style="list-style-type: none"> • Pregnancy test π • Urine dipstick/culture*
	Blood	<ul style="list-style-type: none"> • HIV-1/2 testing • CBC with differential and platelets* • Serum creatinine* • Plasma for archive • HSV 1/2 serology
	Pelvic Samples	<ul style="list-style-type: none"> • NAAT for GC/CT and trichomonas* • Saline/KOH wet mount with pH for candidiasis and/or BV* • Vaginal swabs for microbiota • Vaginal Gram stain • Cervicovaginal fluid (CVF) TFV levels \blacktriangle • CVF for anti-HSV-2 activity \boxtimes • CVF for biomarkers \boxtimes • Cervicovaginal lavage (CVL) for PD and biomarkers \boxtimes
Study Product Supply		<ul style="list-style-type: none"> • Provision of study IVR • Insertion of the provided study IVR • Provision of study IVR use instructions • Offer male condoms*

* If indicated and/or per local standard of care

\blacktriangle Samples to be taken approximately 1 and 4 hours following ring insertion

▫ Samples to be taken prior to ring insertion

π Not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records

7.4 Follow-up Visits

7.4.1 Days 1 and 7 - Visits 3 and 4

Table 6: Days 1 and 7- Visits 3 and 4

Days 1 and 7 - Visits 3 and 4		
Component		Procedure/Analysis
Administrative and Regulatory		<ul style="list-style-type: none"> Review/update locator information Provide reimbursement Schedule next visit/contact
Behavioral/Counseling		<ul style="list-style-type: none"> HIV pre- and post-test counseling* HIV/STI risk reduction counseling* Protocol counseling
Clinical		<ul style="list-style-type: none"> Review/update medical and menstrual history Review/update concomitant medications Perform targeted physical examination* Perform pelvic examination Treat or prescribe treatment for RTI/UTI/STIs* Provide available test results Collect AEs
Laboratory	Urine	<ul style="list-style-type: none"> Pregnancy test* Urine dipstick/culture*
	Blood	<ul style="list-style-type: none"> HIV-1/2 testing* CBC with differential and platelets* Serum creatinine* Syphilis serology* TFV levels
	Pelvic Samples	<ul style="list-style-type: none"> NAAT for GC/CT and trichomonas* Saline/KOH wet mount with pH for candidiasis and/or BV* CVF TFV levels CVF for biomarkers
	Rectal Samples	<ul style="list-style-type: none"> Rectal fluid TFV levels (Day 1 only)
Study Product Supply		<ul style="list-style-type: none"> Offer male condoms*

* If indicated and/or per local standard of care

7.4.2 Day 14 - Visit 5

The MTN-038 cohort will be randomized to provide cervical tissue for assessment of PK at alternate study visits starting with Visit 5 on Day 14. One half of the cohort will be randomized to provide tissue at Visits 5 and 8, and the other half will be randomized to provide tissue at Visits 6 and 9.

Table 7: Day 14 - Visit 5

Day 14 - Visit 5		
Component		Procedure/Analysis
Administrative and Regulatory		<ul style="list-style-type: none"> Review/update locator information Provide reimbursement Schedule next visit/contact
Behavioral/Counseling		<ul style="list-style-type: none"> HIV pre- and post-test counseling* HIV/STI risk reduction counseling* Protocol counseling
Clinical		<ul style="list-style-type: none"> Review/update medical and menstrual history Review/update concomitant medications Perform targeted physical examination* Perform pelvic examination Treat or prescribe treatment for RTI/UTI/STIs* Provide available test results Collect AEs
Laboratory	Urine	<ul style="list-style-type: none"> Pregnancy test* Urine dipstick/culture*
	Blood	<ul style="list-style-type: none"> HIV-1/2 testing* CBC with differential and platelets* Serum creatinine* Syphilis serology* TFV levels
	Pelvic Samples	<ul style="list-style-type: none"> NAAT for GC/CT and trichomonas* Saline/KOH wet mount with pH for candidiasis and/or BV* CVF TFV levels CVF for biomarkers Cervical biopsies for PK‡
	Rectal Samples	<ul style="list-style-type: none"> Rectal fluid TFV levels
Study Product Supply		<ul style="list-style-type: none"> Offer male condoms*

* If indicated and/or per local standard of care

‡ Participants will be randomized to biopsy collection either at Visits 5 and 8 or Visits 6 and 9

7.4.3 Day 28 - Visit 6

Table 8: Day 28 - Visit 6

Day 28 - Visit 6		
Component		Procedure/Analysis
Administrative and Regulatory		<ul style="list-style-type: none"> Review/update locator information Provide reimbursement Schedule next visit/contact
Behavioral/Counseling		<ul style="list-style-type: none"> HIV pre- and post-test counseling* HIV/STI risk reduction counseling* Protocol counseling Collect product use information Collect product preference/acceptability information Behavioral assessment
Clinical		<ul style="list-style-type: none"> Review/update medical and menstrual history Review/update concomitant medications Perform targeted physical examination* Perform pelvic examination Treat or prescribe treatment for RTI/UTI/STIs* Provide available test results Collect AEs
Laboratory	Urine	<ul style="list-style-type: none"> Pregnancy test π Urine dipstick/culture*
	Blood	<ul style="list-style-type: none"> HIV-1/2 testing* AST/ALT* CBC with differential and platelets* Serum creatinine* Syphilis serology* TFV levels
	Pelvic Samples	<ul style="list-style-type: none"> NAAT for GC/CT and trichomonas* Saline/KOH wet mount with pH for candidiasis and/or BV* Vaginal swabs for microbiota Vaginal Gram stain CVF TFV levels CVF for anti-HSV-2 activity CVF for biomarkers Cervical biopsies for PK‡ CVL for PK, PD, and biomarkers
	Rectal Samples	<ul style="list-style-type: none"> Rectal fluid TFV levels
Study Product Supply		<ul style="list-style-type: none"> Offer male condoms*

* If indicated and/or per local standard of care

π Not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records

‡ Participants will be randomized to biopsy collection either at Visits 5 and 8 or Visits 6 and 9

7.4.4 Day 42 - Visit 7

Table 9: Day 42 - Visit 7

Day 42 - Visit 7		
Component		Procedure/Analysis
Administrative and Regulatory		<ul style="list-style-type: none"> Review/update locator information Provide reimbursement Schedule next visit/contact
Behavioral/Counseling		<ul style="list-style-type: none"> HIV pre- and post-test counseling* HIV/STI risk reduction counseling* Protocol counseling
Clinical		<ul style="list-style-type: none"> Review/update medical and menstrual history Review/update concomitant medications Perform targeted physical examination* Perform pelvic examination Treat or prescribe treatment for RTI/UTI/STIs* Provide available test results Collect AEs
Laboratory	Urine	<ul style="list-style-type: none"> Pregnancy test* Urine dipstick/culture*
	Blood	<ul style="list-style-type: none"> HIV-1/2 testing* AST/ALT* CBC with differential and platelets* Serum creatinine* Syphilis serology*
	Pelvic Samples	<ul style="list-style-type: none"> NAAT for GC/CT and trichomonas* Saline/KOH wet mount with pH for candidiasis and/or BV* CVF for biomarkers
Study Product Supply		<ul style="list-style-type: none"> Offer male condoms*

* If indicated and/or per local standard of care

7.4.5 Day 56 - Visit 8

Table 10: Day 56 - Visit 8

Day 56 - Visit 8		
Component		Procedure/Analysis
Administrative and Regulatory		<ul style="list-style-type: none"> Review/update locator information Provide reimbursement Schedule next visit/contact
Behavioral/Counseling		<ul style="list-style-type: none"> HIV pre- and post-test counseling* HIV/STI risk reduction counseling* Protocol counseling Collect product use information Behavioral assessment
Clinical		<ul style="list-style-type: none"> Review/update medical and menstrual history Review/update concomitant medications Perform targeted physical examination* Perform pelvic examination Treat or prescribe treatment for RTI/UTI/STIs* Provide available test results Collect AEs
Laboratory	Urine	<ul style="list-style-type: none"> Pregnancy test π Urine dipstick/culture*
	Blood	<ul style="list-style-type: none"> HIV-1/2 testing* AST/ALT* CBC with differential and platelets* Serum creatinine* Syphilis serology* TFV levels
	Pelvic Samples	<ul style="list-style-type: none"> NAAT for GC/CT and trichomonas* Saline/KOH wet mount with pH for candidiasis and/or BV* Vaginal swabs for microbiota Vaginal Gram stain CVF TFV levels CVF for anti-HSV-2 activity CVF for biomarkers Cervical biopsies for PK and PD\ddagger CVL for PK, PD, and biomarkers
	Rectal Samples	<ul style="list-style-type: none"> Rectal fluid TFV levels
Study Product Supply		<ul style="list-style-type: none"> Offer male condoms*

* If indicated and/or per local standard of care

π Not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records

\ddagger Participants will be randomized to biopsy collection either at Visits 5 and 8 or Visits 6 and 9

7.4.6 PUEV/Early Termination Visit Ring Removal - Visit 9 - Day 91

Table 11: PUEV/Early Termination Visit - Visit 9 - Day 91

PUEV/Early Termination Visit - Visit 9 – Day 91		
Component		Procedure/Analysis
Administrative and Regulatory		<ul style="list-style-type: none"> Review/update locator information Provide reimbursement Schedule next visit/contact
Behavioral/Counseling		<ul style="list-style-type: none"> HIV pre- and post-test counseling HIV/STI risk reduction counseling Protocol counseling Collect product use information Collect product preference/acceptability information Behavioral assessment In-depth interview (IDI) (Subset)♦
Clinical		<ul style="list-style-type: none"> Review/update medical and menstrual history Review/update concomitant medications Perform targeted physical examination* Perform pelvic examination Treat or prescribe treatment for RTI/UTI/STIs* Provide available test results Collect AEs
Laboratory	Urine	<ul style="list-style-type: none"> Pregnancy test π Urine dipstick/culture*
	Blood	<ul style="list-style-type: none"> HIV-1/2 testing CBC with differential and platelets Serum creatinine AST/ALT Syphilis serology* TFV levels∞
	Pelvic Samples	<ul style="list-style-type: none"> NAAT for GC/CT and trichomonas* Saline/KOH wet mount with pH for candidiasis and/or BV* Vaginal swabs for microbiota Vaginal Gram stain CVF TFV levels∞ CVF for biomarkers Cervical biopsies for PK and PD‡
	Rectal Samples	<ul style="list-style-type: none"> Rectal fluid TFV levels∞
Study Product Supply		<ul style="list-style-type: none"> Removal and collection of study IVR Offer male condoms*

* If indicated and/or per local standard of care

∞ Samples to be taken immediately prior to ring removal and approximately 4 hours following ring removal

‡ Participants will be randomized to biopsy collection either at Visits 5 and 8 or Visits 6 and 9

♦ May be scheduled for later date due to visit length and/or to accommodate participant availability

π Not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records

7.4.7 Final Contact - Visit 10 - Day 92

Participants will be encouraged to contact the study clinic if they experience any untoward medical occurrences after the Final Contact visit.

Table 12: Final Contact - Visit 10 - Day 92

Final Contact - Visit 10 - Day 92		
Component		Procedure/Analysis
Administrative and Regulatory		<ul style="list-style-type: none">Review/update locator informationProvide reimbursementSchedule next visit/contact*
Behavioral/Counseling		<ul style="list-style-type: none">HIV pre- and post-test counseling*HIV/STI risk reduction counseling*
Clinical		<ul style="list-style-type: none">Review/update medical and menstrual historyReview/update concomitant medicationsPerform targeted physical examination*Perform pelvic examination*Treat or prescribe treatment for RTI/UTI/STIs*Provide available test resultsCollect AEs
Laboratory	Urine	<ul style="list-style-type: none">Pregnancy test*Urine dipstick/culture*
	Blood	<ul style="list-style-type: none">CBC with differential and platelets*Serum creatinine*TFV levels
	Pelvic Samples	<ul style="list-style-type: none">Saline/KOH wet mount with pH for candidiasis and/or BV*CVF TFV levels
Study Product Supply		<ul style="list-style-type: none">Offer male condoms*

* If indicated and/or per local standard of care

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

7.5.1 Participants Who Become Infected with HIV

If a participant tests positive for HIV after the Enrollment Visit, the participant will be referred to local care and treatment services and may return to the research clinic for additional counseling and other support services, as needed. Continued study participation would be of no added benefit and thus follow-up visits will be discontinued, study product use will cease, and the participant will be considered terminated from the study. Participants who become infected after randomization may be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), as clinically indicated per discussions between IoR and LC. Please reference the MTN-038 SSP Manual for additional details (www.mtnstopshiv.org).

7.5.2 Participants Who Become Pregnant

If a participant becomes pregnant, she will be referred to local health care services and may return to the research clinic for additional counseling, as needed. Continued study participation would be of no added benefit to the participant, thus follow-up visits and procedures will be discontinued and the participant will be considered terminated from the study. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained; see [Section 9.8](#) for additional details. Participants who become pregnant while on study product will be offered enrollment in MTN-016 (www.mtnstopshiv.org), provided their study site is taking part in MTN-016, which includes follow-up throughout the pregnancy and for the first year of the infant's life. For participants who do not enroll in MTN-016, the study site will make every reasonable effort to contact participants and collect infant outcome at approximately one year after delivery for those pregnancies that result in live birth. For additional details regarding obtaining pregnancy outcome, please reference the MTN-038 SSP Manual (www.mtnstopshiv.org).

7.5.3 Participants Who Permanently Discontinue Study Product for Other Reasons

For participants who permanently discontinue study product use for any clinician-initiated reason other than HIV infection or pregnancy, site investigators may, after consultation with the PSRT and MTN-038 Management Team, decide to discontinue study follow-up visits and procedures. Participants will, however, be asked to complete all the procedures scheduled to occur at the PUEV/Early Termination Visit (Visit 9), if willing.

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

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

- Pelvic exams*
- Sample collection for TFV levels
- Sample collection for anti-HSV-2 activity
- Sample collection for PK, PD, and biomarkers
- Swabs for microbiota
- Collection of blood for safety assessments*
- Behavioral assessments
- Protocol counseling will be modified

**Unless required for AE follow-up*

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

Note: The MTN-038 Management Team, in consultation with the MTN Pharmacology Core, may provide guidance to the site regarding a modified study visit schedule to ensure PK samples are collected at the appropriate time points and/or omitted if the collection of samples would not be anticipated to yield analyzable data. Participants' duration of use and timing of study product permanent discontinuation will be factored into a modified schedule. Refer to the MTN-038 SSP Manual for additional details.

7.6 Interim Visits

Interim visits may be performed at any time during the study and any visit procedures may be conducted as indicated. All interim contacts and visits will be documented in participants' study records. If a participant misses a visit (e.g., presents to the clinic outside of the visit window), she can return for an interim visit to make up certain missed visit procedures and specimen collections. Refer to the MTN-038 SSP Manual for additional details.

7.7 Protocol Counseling: Adherence and Contraception Counseling

Study product and protocol adherence counseling will be provided to all participants in the study. Contraception counseling will be provided to all participants beginning at the Screening Visit. Persons who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records are not required to receive contraceptive counseling. Counseling will be provided in accordance with standard methods, and will include reminders regarding concomitant medication and behavioral restrictions prior to and following collection of biopsies and CVF.

7.8 Pharmacokinetics

The entire MTN-038 cohort will provide plasma for assessment of TFV levels at Visits 3, 4, 5, 6, 8, 9 and 10, CVF for assessment of TFV levels at Visits 2, 3, 4, 5, 6, 8, 9 and 10, and rectal fluid for assessment of TFV levels at Visits 3, 5, 6, 8, and 9. Half of all participants will be randomized to provide cervical tissue for assessment of PK at Visits 5 and 8, and the other half will be randomized to provide cervical tissue for PK at Visits 6 and 9.

Detailed instructions are provided in the MTN-038 SSP Manual available at <http://www.mtnstopshiv.org>.

Table 13: PK, PD, and Biomarkers Specimen Collection Schedule

Visit	Specimens Collected for PK	Specimens Collected for PD and/or to Assess Biomarkers of Mucosal Safety
Visit 2 – Enrollment (Day 0)	<ul style="list-style-type: none"> • Cervicovaginal fluid (CVF) ▲ 	<ul style="list-style-type: none"> • Cervicovaginal lavage (CVL) ☐ • CVF ☐
Visit 3 - Day 1 Visit 4 - Day 7 Visit 5 - Day 14	<ul style="list-style-type: none"> • Plasma • CVF • Rectal fluid (Visits 3 and 5 only) • Cervical tissue ‡ (Visit 5 only) 	<ul style="list-style-type: none"> • CVF
Visit 6 - Day 28	<ul style="list-style-type: none"> • Plasma • CVF • Rectal fluid • Cervical tissue ‡ • CVL 	<ul style="list-style-type: none"> • CVL • CVF
Visit 7 – Day 42		<ul style="list-style-type: none"> • CVF
Visit 8 - Day 56	<ul style="list-style-type: none"> • Plasma • CVF • Rectal fluid • Cervical tissue ‡ • CVL 	<ul style="list-style-type: none"> • CVL • CVF • Cervical tissue ‡
Visit 9 - PUEV/Early Termination Visit (Day 91)	<ul style="list-style-type: none"> • Plasma ∞ • CVF ∞ • Rectal fluid ∞ • Cervical tissue ‡ 	<ul style="list-style-type: none"> • Cervical tissue ‡ • CVF
Visit 10 - Final contact (Day 92)	<ul style="list-style-type: none"> • Plasma • CVF 	

☐ Collected prior to ring insertion

▲ To be collected at approximately 1 hour and 4 hours following ring insertion

‡ Participants will be randomized to biopsy collection either at Visits 5 and 8 or Visits 6 and 9

∞ To be collected immediately prior to ring removal and approximately 4 hours following ring removal

7.9 Behavioral Measures

Behavioral Assessment

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

vaginal compartment. A subset of these behaviors will be assessed in follow-up questionnaires at Visit 6 (Day 28), Visit 8 (Day 56), and Visit 9 (PUEV/Early Termination Visit). Measures used previously in other microbicide trials will be employed.

Product Adherence Assessment

Key adherence measures will be captured by CASI and by CRFs to ensure maximum confidentiality of responses. Product use information will be collected at Visit 6 (day 28), Visit 8 (Day 56), and Visit 9 (PUEV/Early Termination Visit). The questions will assess study IVR use, report of frequency of study IVR removal/expulsions (voluntary and involuntary) and duration without IVR inserted in the vagina. Clinician-initiated VR removals for the purpose of clinical examination are to be excluded from consideration during product adherence assessment. A series of questions will ask if the study IVR was out, whether it was removed or expelled, under what circumstances or conditions it was removed or expelled, and whether it was re-inserted. A combination of self-administered and interviewer-administered questionnaires will be employed to capture the above information. Study staff will provide participants with guidance on strategies to optimize recall of relevant behavioral and adherence data. This quantitative assessment will be modeled on the adherence assessment for protocols MTN-036 (www.mtnstopshiv.org) and other previous trials of the DPV ring (MTN-013, MTN-020 and IPM 027 [<http://www.ipmglobal.org/>]). Additionally, at all visits in which a pelvic exam is performed, clinicians will assess whether the IVR is in place through visualization on speculum exam (or bimanual exam if needed) and record this assessment on a CRF.

Product Preference/Acceptability Assessment

A product preference/acceptability questionnaire will be administered by CASI to participants at the Enrollment Visit and Visit 6 (Day 28), with a more thorough questionnaire administered at Visit 9 (PUEV/Early Termination Visit). HIV prevention product preference will also be assessed at the PUEV/Early Termination Visit. This questionnaire includes structured questions about the participant's attitude related to the IVR (product characteristics; likes and dislikes concerning the IVR), her experiences using the IVR (e.g., genitourinary discomfort, ease of use/removal, displacement, willingness to use during menstruation, willingness to use in the future), effect on sex, and partner's reactions. Measures used previously in MTN-036 and other microbicide trials will be employed.^{26,27}

In-Depth Interview

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

transcribed for analysis. The interview notes, recording and transcript will be considered as source documentation.

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

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

7.10 Clinical Evaluations and Procedures

Physical exams will include the following assessments:

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

**may be omitted during targeted physical examinations*

Pelvic Examination and Specimen Collection

Pelvic examinations will be conducted per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at <http://www.conrad.org/publications-13.html>.

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

The required sequence of procedures and specimen collection performed during pelvic exams will be specified in the MTN-038 SSP Manual.

7.11 Laboratory Evaluations

Local Laboratory

- Urine
 - Pregnancy test
 - Dipstick/culture
- Blood
 - AST/ALT
 - CBC with differential and platelets
 - Serum creatinine
 - HIV-1/2 testing (including HIV-1/2 confirmation testing)
 - Syphilis serology
 - Hepatitis B surface antigen
- Pelvic
 - Pap test
 - Saline/KOH wet mount with pH for candidiasis and/or BV
 - NAAT for GC/CT and trichomonas

Network Laboratory Center (LC)

- Blood
 - Plasma for TFV levels
 - Confirmation HIV-1/2 testing for seroconversion
 - HIV-1 resistance tests for confirmed seroconverters
 - HSV 1/2 serology
 - Plasma for archive
- Pelvic
 - CVF for TFV levels
 - CVF for biomarkers
 - CVL for PK, anti-HIV PD, biomarkers
 - Cervical tissue for PK and anti-HIV PD
 - Vaginal swabs for microbiota
 - Gram stain of vaginal smear
- Rectal
 - Rectal fluid for TFV levels

Designated Laboratory

- Study Product
 - Used study IVR residual drug level assessment (TFV)
 - Used study IVR biomarker assessment (residual glycerin content and other bioassays)
- Anti-HSV-2 activity
 - CVF for anti-HSV-2 activity

Once all required study analyses of collected specimens are complete, any remaining samples may be shipped to the MTN LC for use in study-related quality assurance and quality control testing. If study samples will be used for assay validation or proficiency testing that is not study related, all participant identifiers will be removed from the samples prior to use. Specimens obtained from participants who do not consent to long term storage will not be used for assay validation or proficiency testing purposes.

7.12 Specimen Management

Each study site will adhere to the standards of good clinical laboratory practice (<https://www.niaid.nih.gov/sites/default/files/gclp.pdf>) in accordance with current US Division of AIDS (DAIDS) Laboratory Requirements, MTN-038 Study Specific Procedures Manual (<http://www.mtnstopshiv.org>) and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to standardize procedures. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens. Further, as part of quality control, researchers may need to look at short pieces of non-coding repetitive DNA sequence (3-7 base pairs) from blood in the event of sample mix-up. This test will only let researchers know the number of times this short segment is repeated and not specific genes or specific sequences of base pairs. This sequence element does not contain any information about genes, and therefore researchers will not be able to identify if participants are predisposed to specific diseases or any other genetic information based on this information. This test will be an important tool for distinguishing whether two samples collected at the same or different time points are likely from the same person. The test will only be used as part of a sample investigation with the knowledge of the site in situations where a known or suspected sample mix-up has occurred. No genetic testing (limited or genome-wide) is planned on leftover samples that are stored for the purposes of future research.

7.13 DAIDS Laboratory Oversight

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

7.14 Biohazard Containment

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

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

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

8.2 Clinical Data and Safety Review

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

MTN SDMC staff will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. AE reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer and SDMC staff, and the CONRAD safety physician for review.

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

The Study Monitoring Committee (SMC) will review participant safety data as part of their regular reviews (see [Section 10.7.1](#)), since no Data and Safety Monitoring Board oversight is planned for MTN-038. The SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Members of the SMC will be independent investigators with no interest (financial or otherwise) in the outcomes of this study. If at any time a decision is made to discontinue enrollment and/or study product use in all participants, DAIDS will notify the FDA and the Site IoRs will notify the responsible IRBs expeditiously.

The MTN SMC will also conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, and study or lab issues. These reviews will take place approximately every 4-6 months, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant administered an 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 beginning at the time of enrollment (i.e., once a participant is randomized) through the termination visit. The term “investigational product” for this study refers to all study products.

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

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

Please note:

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

8.3.2 Serious Adverse Events

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

- Results in death
 - Is life-threatening
 - Results in persistent or significant disability/incapacity
 - Is a congenital anomaly/birth defect
 - Requires inpatient hospitalization or prolongation of existing hospitalization
- Note:* Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event. Thus, hospitalization in the absence of an AE is not regarded as an AE, and is not subject to expedited reporting. The following are examples of hospitalization that are not considered to be AEs:

- Protocol-specified admission (e.g., for procedure required by study protocol)
- Admission for treatment of target disease of the study, or for pre-existing condition (unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator)
- Diagnostic admission (e.g., for a work-up of an existing condition such as persistent pretreatment lab abnormality)
- Administrative admission (e.g., for annual physical)
- Social admission (e.g., placement for lack of place to sleep)
- Elective admission (e.g., for elective surgery)

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

8.3.3 Adverse Event Relationship to Study Product

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

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

8.4 Adverse Event Reporting Requirements

8.4.1 Expedited Adverse Event Reporting to DAIDS

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

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

For questions about DAERS, please contact NIAID CRMS Support at

CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

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

8.4.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study
- The study agent for which expedited reporting is required is the TFV IVR

8.4.3 Grading Severity of Events

The grading of severity of events and the reporting period will be the same as for all AEs, as described in [Section 8.3.1](#). The most current Division of AIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, November 2007), will be used and are available on the RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>.

8.4.4 Expedited AE Reporting Period

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

After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.5 Pregnancy and Pregnancy Outcomes

Pregnant women are excluded from this study.

A participant who is pregnant after enrollment will continue to be followed until the pregnancy outcome is ascertained. A participant who becomes pregnant during the study will have study product discontinued and will be terminated from the study. Please see [Section 9.8](#) for additional details.

8.6 Regulatory Requirements

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

8.7 Social Harms Reporting

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the PSRT and responsible site IRBs according to their individual requirements.

9 CLINICAL MANAGEMENT

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

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

9.1 Grading System

AE severity grading is described in [Section 8.4.3](#).

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

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

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

- Acquisition of HIV-1/2 infection; such participants will not resume product use at any time. The study IVR must be held beginning immediately upon recognition of the first reactive rapid HIV test.
- Allergic reaction to the IVR
- Pregnancy
- Breastfeeding
- Non-therapeutic injection drug use

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

- Reported use of PEP for HIV exposure
- Reported use of PrEP for HIV prevention
- Use of heparin, Lovenox®, warfarin, Plavix® (clopidogrel bisulfate), or other anticoagulant
- Any clinical study product hold lasting more than 7 days
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee. (May result in temporary hold or permanent discontinuation)

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

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

Grade 1 or 2

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

Grade 3

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

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

Grade 4

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

9.5 Sexually Transmitted Infection/Reproductive Tract Infection

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

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

9.6 Management of Specific Genital Events

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

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

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

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

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

Unexpected genital bleeding

- Continue study IVR 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 IVR use.

Genital petechia(e) and genital ecchymosis

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

9.7 HIV Infection

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

9.8 Pregnancy

Pregnancy testing will be performed at designated study visits and participants will be encouraged to report all signs or symptoms of pregnancy to study staff. Pregnancy testing is not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records. The IoR/designee will counsel any participant who becomes pregnant regarding possible risks to the fetus according to site

SOPs. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

A participant who becomes pregnant during the study will have study product discontinued and will be terminated from the study, as per [Section 7.5.2](#). A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Pregnancy outcomes will be reported on relevant CRFs. Pregnancy outcomes will not be expeditiously reported to CONRAD and the DAIDS Medical Officer (MO) unless there is an associated AE in the pregnant participant that meets expedited reporting criteria or the pregnancy results in a congenital anomaly meeting the DAIDS EAE Manual (Version 2.0, January 2010) guidelines for expedited reporting.

A participant who becomes pregnant during study participation may be offered participation in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study, at sites participating in MTN-016. This registry study captures pregnancy outcomes as well as infant health information (including growth) to evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy. For participants who do not enroll in MTN-016, the study site will make every reasonable effort to contact participants and collect infant outcome at approximately one year after delivery for those pregnancies that result in live birth.

9.9 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The IoR/designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if CONRAD, NIAID, MTN, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is a Phase 1, two-arm, multi-site, randomized (2:1), placebo-controlled trial of a polyurethane reservoir IVR containing the active ingredient TFV. A total of approximately 48 healthy, HIV-uninfected participants will be enrolled and randomized 2:1 (32 in the active arm and 16 in the placebo arm) to use a study IVR. Participants will use the study IVR continuously for approximately 91 days.

10.2 Study Endpoints

Consistent with the primary study objective to assess the PK of the 1.4 g TFV IVR when used continuously for 91 days, the following endpoints will be assessed:

- TFV concentrations in plasma
- TFV concentrations in CVF
- TFV concentrations in rectal fluid
- TFV and TFV-DP concentrations in cervical tissue

Consistent with the primary study objective to assess safety of the 1.4 g TFV IVR when used continuously for 91 days, the primary safety endpoints are the proportion of participants with the following:

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

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

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

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

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

10.3 Primary Study Hypotheses

- Plasma, CVF, and rectal fluid TFV levels and cervical tissue TFV and TFV-DP levels will be measurable in all participants
- Continuous exposure to TFV due to sustained release from the 1.4 g TFV IVR for 91 days will be safe

10.4 Sample Size and Power Calculations

10.4.1 Primary Endpoints

The proposed total sample size is approximately N=48 adult participants. The sample size is based upon the size of similar Phase 1 studies of vaginal microbicide products.

As a means to characterize the statistical properties of this study, Table 14 below presents the probability of observing thirty or more, thirty-one or more, or thirty-two participants with detectable PK levels (or a level above a specified threshold value) among the 32 participants in the active arm given a true event rate. For example, if the true rate of detection (or rate above a specified threshold) among participants using a ring is 99% then the probability we will see 31 or more participants with detectable PK levels is 96%.

Table 14: Analysis of PK Event Frequency

“True” Event Rate (PK Detectable or above a specified threshold value)	P (≥ 30 events n=32)	P (≥ 31 events n=32)	P (32 events n=32)
90%	0.37	0.16	0.03
95%	0.79	0.52	0.19
99%	>0.99	0.96	0.72

Table 15 below presents the probability of observing zero, one or more and two or more safety events among the 32 participants in the active arm given a true event rate. For example, if the true rate of a safety event among participants using a ring is 10% then the probability we will see 1 or more participants with this event is 97%.

Table 15: Analysis of Safety Event Frequency

“True” Event Rate (Safety Event)	P (0 events n=32)	P (≥ 1 events n=32)	P (≥ 2 events n=32)
1%	0.72	0.28	0.04
5%	0.19	0.81	0.48
10%	0.03	0.97	0.84

An alternative way of describing the statistical properties of the study design is in terms of the 95% confidence interval (95% CI) for the true rate based on the observed data. Table below shows the exact 2-sided 95% CIs for the probability of an event based on a particular observed rate. If none of the 32 participants in the active arm experience a safety event, the 95% exact 2-sided upper confidence bound for the true rate of such events in that study arm is 11%. Similarly, if all 32 participants in the active arm have detectable PK, the 95% exact 2-sided lower confidence bound for the true rate of PK detection is 89%.

Table 16: Precision of Exact 2-sided 95% CIs for Observed Event Rates

Observed Event Rate	Exact 2-sided 95% CI (n=12)
32/32 (100%)	89%, 100%
30/32 (94%)	79%, 99%
25/32 (78%)	60%, 91%
16/32 (50%)	32%, 68%
10/32 (31%)	16%, 50%
3/32 (9%)	2%, 25%
0/32 (0%)	0%, 11%

An additional aim of the study is to compare the safety between the active and placebo IVR arms. Assuming a one-sided test with $\alpha=0.05$ and Fisher’s Exact Test, Table below provides the difference in the rates of safety events (proportion of participants experiencing the safety event of interest) between the active IVR arm and the placebo IVR arm that is detectable with 90% power for a given rate in the placebo IVR arm. For example, if the true rate of a given safety endpoint in the placebo IVR arm is 12.5% (2 of 16 participants experience a safety event), the proposed sample size provides 90% power to exclude safety endpoint rates greater than 57.5% (51.9% with 80% power). Hence, while comparisons will be made between the active IVR arm and the placebo IVR arm, the study will only have power to detect large differences in safety event rates.

Table 17: Safety Event Rates that Provide 90% Power for Testing Equality of Safety Event Rates

Rate in Placebo IVR Arm	Rate in Active IVR Arm
6.3%	48.7%
12.5%	57.5%
18.8%	65.2%
25.0%	71.9%
31.3%	78.0%

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

10.4.2 Secondary Endpoints

Adherence will be measured by the percentage of participants who keep the IVR inserted at all times in the vagina over the course of 91 days. (Clinician-initiated VR removals for the purpose of clinical examination will be excluded from consideration.) A sample size of 48 participants will provide a precision of 13.0% (i.e., half the width of the 95% confidence interval) assuming an observed adherence of 75%.

Overall acceptability will be measured by the degree (on a scale of 1 to 10) to which participants like or dislike using the IVR over the course of 91 days. Previous studies using such a scale indicate that the standard deviation of this score is approximately 2.4. Assuming a similar standard deviation and 32 participants in the active IVR arm and 16 in the placebo arm, the study will have 90% power to detect a difference in the acceptability score of 2.65.²⁸

10.5 Participant Accrual, Follow-up, and Retention

Based on previous studies of vaginal products with similar eligibility requirements, the accrual of 48 eligible participants will take approximately 6-9 months. Participants lost to follow-up and/or on temporary hold or permanent product discontinuation will not be replaced. However, every effort will be made to complete their regularly scheduled safety evaluations. Additionally, participants who are found to be HIV-infected and/or pregnant after enrollment will be terminated from the study and will not be replaced. Each site will target retention of 95% of enrolled participants over the 92-day follow-up period.

10.6 Randomization

Participants will be randomized in a 2:1 ratio to the active and placebo arms of the study. The 2:1 ratio of active to placebo arms is to allow for the collection of additional safety and PK endpoints in the TFV IVR arm. Study arm randomization will be stratified by site to ensure balanced assignment of products at each site. In addition, approximately 24 participants will be randomly selected for IDIs. Finally, the timing of biopsies will also be randomly assigned. Biopsy schedule randomization will be ideally balanced between active and placebo groups and in a 1:1 ratio of Day 14 and Day 56 to Day 28 and Day 91.

The randomization schemes will be generated and maintained by the MTN SDMC and will be specified in the MTN-038 SSP manual.

10.7 Data and Safety Monitoring and Analysis

10.7.1 Study Monitoring Committee

Data and Safety Monitoring Board oversight is not planned for this study. The MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, study or lab issues, and a closed safety data report to voting SMC members. The review will take place approximately every 4-6 months, or as needed. At the time of this review, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. For further information regarding the SMC, please reference the MTN Manual of Operational Procedures (www.mtnstopshiv.org).

10.7.2 Primary Analyses

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

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

Pharmacokinetic Analysis

The proportion of participants with detectable drug levels in the active arm and the measured drug concentration levels will be summarized using descriptive statistics and graphics. Routine PK parameters will also be used to describe drug concentrations where appropriate.

Safety Analysis

All visits in which a woman has been exposed to the study product will be included in the primary analyses of safety. Secondary intent to treat analyses may also be performed. To assess genitourinary safety, the number and the percentages of participants experiencing each safety endpoint (see [Section 10.2](#)) will be tabulated by study arm. Each participant will contribute once in each category (i.e., only for highest severity AE for each

participant) for the calculation of event rates. Exact binomial confidence intervals will be calculated for each safety endpoint for each arm and Fisher's Exact test used to test for differences in event rates between the drug containing IVR arm and the placebo IVR arm.

10.7.3 Secondary Analyses

Adherence Analysis

To assess participant adherence to the IVR, the proportion of participants who reported keeping the study IVR inserted at all times during the 91 days will be calculated along with a 95% confidence interval. (Clinician-initiated VR removals for the purpose of clinical examination will be excluded from consideration during product adherence analysis.) For participants who were not fully adherent, the number of self-reported removal/expulsion events and average duration of these events will be reported. Additionally, the average cumulative period of time during the study period when the study IVR was outside the vagina will be calculated. Number, type and circumstances of expulsions (voluntary and involuntary) will be described.

Acceptability Analysis

To assess acceptability of the study IVR, the 10-point acceptability scale will be summarized by calculating the mean, standard deviation, and 95% CI overall, and by study arm. In addition, acceptability between the active and placebo arms will be compared using the t-test or Mann-Whitney U test depending on the distribution of the data.

The acceptability analysis will be supplemented by presenting the above proportion by randomization arm along with its corresponding 95% confidence interval.

10.7.4 Missing Data

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

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

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

Research Triangle Institute will manage all qualitative data for the study. Qualitative data will be collected, stored and analyzed by Research Triangle Institute. Audio files from interviews conducted by qualitative analysts will be stored securely on HIPAA compliant servers. The audio files will be transcribed by an external transcription service and sent only over a secure file transfer protocol site. The transcriptionist will follow all procedures outlined in the Data Use Agreement with Research Triangle Institute. Transcripts will be stored securely on HIPAA compliant servers. The paper notes taken by the qualitative analyst during the interviews will be saved in a locked files cabinet in the Research Triangle Institute office.

11.2 Source Documents and Access to Source Data/Documents

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

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations regarding testing investigational products, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval for the study product being tested for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US FDA is notified.

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

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with current DAIDS policies (<https://www.niaid.nih.gov/sites/default/files/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 may visit the sites to do the following:

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

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

13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make every effort to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR/designee will have obtained IRB approval and the protocol will have been submitted to the FDA. The IoR/designee will permit audits by the NIH, CONRAD, the FDA, OHRP, MTN LOC, IRBs, SDMC, and other local, US or international regulatory authorities or any of their appointed agents.

13.1 Institutional Review Boards/Ethics Committees

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

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

13.2 Protocol Registration

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

Site-specific informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

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

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

13.3 Study Coordination

DAIDS holds the Investigational New Drug (IND) application for this study. Assignment of sponsor responsibilities for this study will be specified in a Clinical Trial Agreement (CTA) executed by NIAID and CONRAD.

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

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

13.4 Risk Benefit Statement

13.4.1 Risks

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

Vaginal Fluid Collection

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

Rectal Fluid Collection

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

Pelvic Examination and Procedures

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

Cervical Biopsy Collection

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

Phlebotomy

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

Other Risks

Being tested for HIV, HSV and STIs and waiting for test results may cause worry, sadness or depression. Provision of positive test results has been associated with depression, suicidal ideation, and denial as well as social isolation. Trained counselors will be available to help participants deal with these feelings.

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

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

Participants who take part in an IDI may be asked questions about their study product use, vaginal and menstrual hygiene, and sexual practices. These questions may make some participants uncomfortable.

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because 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, communities, and/or employer(s).

Risks Associated with Vaginal Rings

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

Toxic shock syndrome has been reported with currently marketed contraceptive VRs, though a causal relationship between the two has not been established.²⁹ As with any vaginally retained product, the possibility of toxic shock syndrome, although rare, exists. Detailed information regarding the plan for diagnosis and management of this condition should it arise is provided in the MTN-038 SSP Manual.

Risks Associated with Tenofovir

The following side effects have been associated with the use of TFV in oral tablet form:

- Upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness
- Dizziness
- Depression
- Headache
- Abdominal pain
- Worsening or new kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas and liver. Symptoms for liver problems may include jaundice, dark urine, stomach pain, loss of appetite, upset stomach or vomiting, pale colored stools, and itchy skin
- Shortness of breath
- Rash
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Muscle pain and muscle weakness
- Nucleotide Analogue: Lactic acidosis and severe hepatomegaly with steatosis that may result in liver failure, other complications or death have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
- Sleeping problems

The following possible side effects have been associated with the use of vaginal rings containing TFV in previous studies:

- Headache
- Vulvovaginal pruritus
- Vulvovaginal pain

- Bladder discomfort
- Vaginal discharge
- Vaginal erythema
- Vaginal and cervical ulceration

13.4.2 Benefits

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

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

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to screening. Written informed consent also will be obtained for long-term specimen storage and possible future testing. Consent for long-term specimen storage is not required for study participation. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (<https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf>). 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 SSP manual.

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

- The unknown safety and unproven efficacy of the 1.4 g TFV IVR
- Randomization and the importance of participants in both of the study groups to the success of the study
- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The real yet limited benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

13.6 Participant Confidentiality

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

All study-related information will be stored securely. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers to identifying information will be stored in a separate, locked file in an area with limited access. After receiving appropriate approval, all study documents/data will be properly disposed of, including the proper destruction and/or deletion of paper files, electronic study data, and electronic documents. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the US Federal Government, including the US FDA, OHRP, NIH, and/or contractors of the NIH, and other local, US or international regulatory authorities
- Representatives of CONRAD and PPD
- Representatives of the MTN LOC, SDMC, and/or LC
- Study staff

- Site IRBs

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

13.7 Special Populations

13.7.1 Pregnant Women

Women who test positive for pregnancy at the Screening or Enrollment Visit will not be eligible to participate in this study. Should a participant test positive for pregnancy after Enrollment, a product discontinuation will be implemented. Follow-up will be completed and data collected per [Section 7.5.2](#). Please refer to [Section 9.8](#) for further details. During the informed consent process, participants will be informed that the study IVR is not proven to be an effective method of contraception and the effects of the study IVR on a developing human fetus are unknown.

13.7.2 Children

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

13.8 Compensation

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

13.9 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV-1/2 identified among study participants to health authorities. Participants will be made aware of reporting requirements during the informed consent process.

13.10 Access to HIV-related Care

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled

participants at each follow-up HIV testing time point. Testing will be performed in accordance with the algorithm in [Appendix II](#). Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will emphasize the unknown efficacy of the study products in preventing HIV infection. In accordance with the policies of the NIH, participants must receive their HIV test results to take part in this study.

13.10.1 Care for Participants Identified as HIV-Positive

An individual who has been identified as infected with HIV will be managed or referred for management according to the local standard of care. Should a participant test positive for HIV after the Enrollment Visit, follow-up procedures will be performed as per [Section 7.5.1](#).

13.11 Study Discontinuation

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

14 PUBLICATION POLICY

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

15 APPENDICES

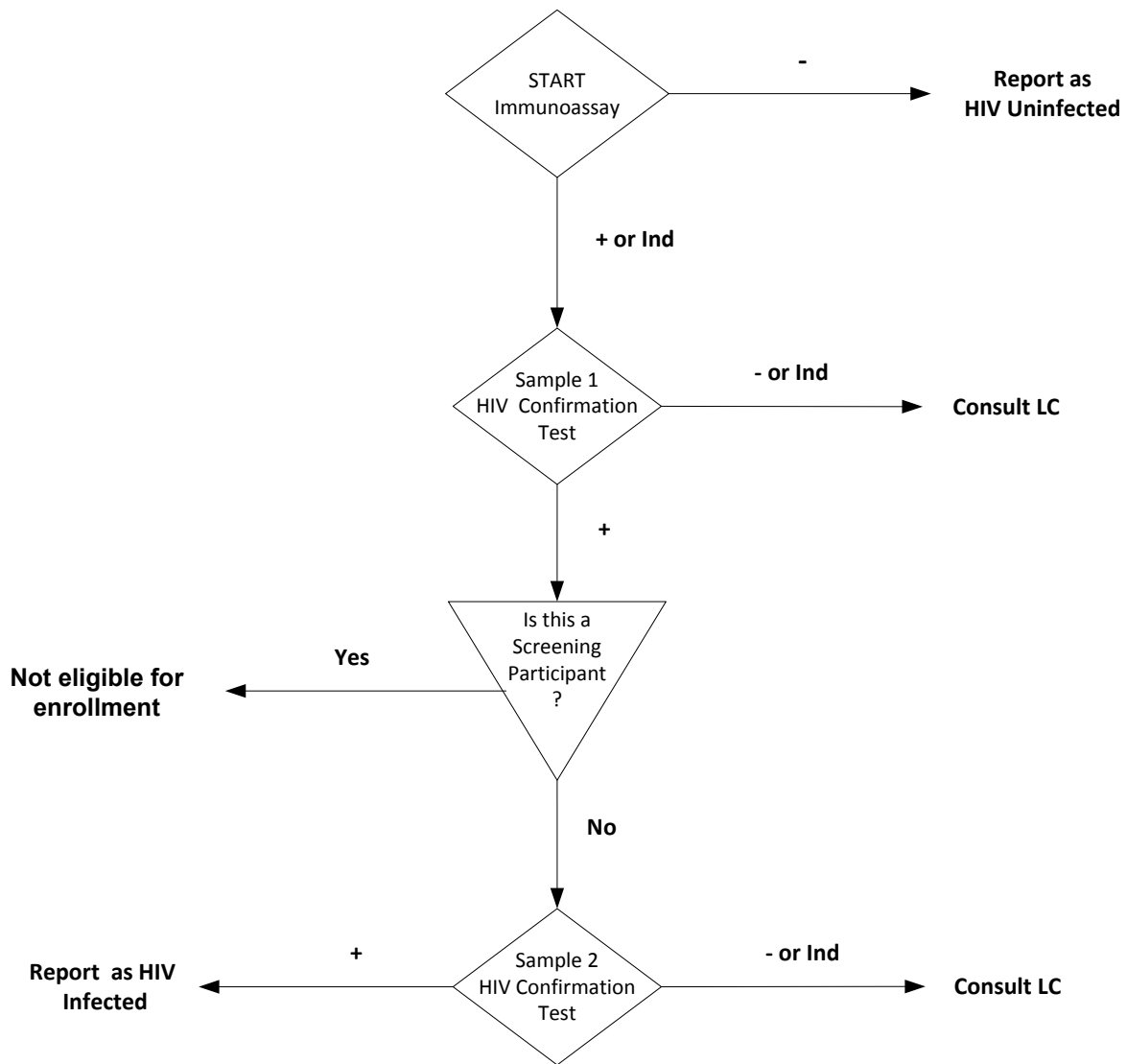
APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	Visit 1 SCR	Visit 2 ENR (Day 0)	Visit 3, 4 (Days 1, 7)	Visit 5 (Day 14)	Visit 6 (Day 28)	Visit 7 (Day 42)	Visit 8 (Day 56)	Visit 9 PUEV/Early Termination (Day 91)	Visit 10 Final Contact (Day 92)
ADMINISTRATIVE AND REGULATORY									
Obtain written informed consent(s)	X								
Assign a unique Participant Identification (PTID) number	X								
Assess and/or confirm eligibility	X	X							
Collect demographic and background information	X								
Collect/review/update locator information	X	X	X	X	X	X	X	X	X
Randomization to product and biopsy schedule		X							
Provide reimbursement	X	X	X	X	X	X	X	X	X
Schedule next visit/contact	*	*	X	X	X	X	X	X	*
BEHAVIORAL/COUNSELING									
HIV pre- and post-test counseling	X	X	*	*	*	*	*	X	*
HIV/STI risk reduction counseling	X	X	*	*	*	*	*	X	*
Protocol counseling	X	X	X	X	X	X	X	X	
Collect product use information					X		X	X	
Collect product preference/acceptability information		X			X			X	
Behavioral assessment		X			X		X	X	
In-depth interview (IDI)								X♦ (subset)	
CLINICAL									
Collect medical eligibility information (including exclusionary conditions and medications)	X	X							
Collect/review/update medical/menstrual history	X	X	X	X	X	X	X	X	X
Collect/review/update concomitant medications	X	X	X	X	X	X	X	X	X
Perform physical exam (Targeted at Visits 2-10)	X	X	*	*	*	*	*	*	*
Perform pelvic exam	X	X	X	X	X	X	X	X	*
Treat or prescribe treatment for RTI/UTI/STIs	*	*	*	*	*	*	*	*	*
Digital exam by clinician to check IVR placement		X							
Provide available test results	X	X	X	X	X	X	X	X	X
Collect AEs			X	X	X	X	X	X	X

		Visit 1 SCR	Visit 2 ENR (Day 0)	Visit 3, 4 (Days 1, 7)	Visit 5 (Day 14)	Visit 6 (Day 28)	Visit 7 (Day 42)	Visit 8 (Day 56)	Visit 9 PUEV/Early Termination (Day 91)	Visit 10 Final Contact (Day 92)
LABORATORY										
URINE	Pregnancy test	X π	X π	*	*	X π	*	X π	X π	*
	Urine dipstick/culture	*	*	*	*	*	*	*	*	*
BLOOD	HIV-1/2 testing	X	X	*	*	*	*	*	X	
	Plasma for archive		X							
	AST/ALT	X				*	*	*	X	
	CBC with differential and platelets	X	*	*	*	*	*	*	X	*
	Serum creatinine	X	*	*	*	*	*	*	X	*
	Hep B surface antigen	X								
	Syphilis serology	X		*	*	*	*	*	*	
	HSV 1/2 serology		X							
	TFV levels			X	X	X		X	X [∞]	X
PELVIC	NAAT for GC/CT and trichomonas	X	*	*	*	*	*	*	*	
	Saline/KOH wet mount with pH for candidiasis and/or BV	*	*	*	*	*	*	*	*	*
	Pap test	X [^]								
	Vaginal swabs for microbiota		X			X		X	X	
	Vaginal Gram stain		X			X		X	X	
	CVF anti-HSV-2 activity		X [□]			X		X		
	CVF TFV levels		X [▲]	X	X	X		X	X [∞]	X
	CVF for biomarkers		X [□]	X	X	X	X	X	X	
	CVL for PK, PD, and biomarkers		X [□] (PD and biomarkers only)			X		X		
RECTAL	Cervical biopsies for PK				X [‡]	X [‡]				
	Cervical biopsies for PK and PD							X [‡]	X [‡]	
	Rectal fluid TFV levels			X (Day 1 only)	X	X		X	X [∞]	
STUDY PRODUCT SUPPLY										
	Provision of study IVR		X							
	Insertion of the provided study IVR		X							
	Provision of study IVR use instructions		X							
	Removal and collection of study IVR								X	
	Offer male condoms	X*	X*	X*	X*	X*	X*	X*	X*	X*

	Visit 1 SCR	Visit 2 ENR (Day 0)	Visit 3, 4 (Days 1, 7)	Visit 5 (Day 14)	Visit 6 (Day 28)	Visit 7 (Day 42)	Visit 8 (Day 56)	Visit 9 PUEV/Early Termination (Day 91)	Visit 10 Final Contact (Day 92)
<p>X required</p> <p>* If indicated and/or per local standard of care</p> <p>^ If participant [over age 21] is unable to provide documentation of a satisfactory Pap test within 3 years prior to enrollment</p> <p>▲ Samples to be taken approximately 1 and 4 hours following ring insertion</p> <p>∞ Samples to be taken immediately prior to ring removal and approximately 4 hours following ring removal</p> <p>▣ Samples to be taken prior to ring insertion</p> <p>‡ Participants will be randomized to biopsy collection either at Visits 5 and 8 or Visits 6 and 9</p> <p>◆ May be scheduled for later date due to visit length and/or to accommodate participant availability</p> <p>π Not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records</p>									

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



Ind: Indeterminate test results
LC: Laboratory Center

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

**SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH**

**MTN-038
Version 1.0
July 11, 2018**

**A Phase 1, Randomized Pharmacokinetic and Safety Study of a 90 Day
Intravaginal Ring Containing Tenofovir**

PRINCIPAL INVESTIGATOR: [Sites to insert]

PHONE: [Sites to insert]

SHORT TITLE: PK and Safety Study of a 90 Day Vaginal Ring Containing Tenofovir

INFORMED CONSENT

IMPORTANT INFORMATION ABOUT THE RESEARCH STUDY

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

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

Approximately 48 people will participate at three study sites in the United States. This study is sponsored by the US National Institutes of Health (NIH) and conducted by the Microbicide Trials Network (MTN). At this site, the person in charge of this study is ***[INSERT NAME OF PRINCIPAL INVESTIGATOR]***.

Important things you should know:

- The study products in this clinical trial are two intravaginal rings (IVR). One contains 1.4 g tenofovir (TFV), an anti-HIV medication, and the other is a placebo. The placebo ring has a similar appearance, size and make-up to the TFV IVR but does not contain study drug or active ingredients.
- The purposes of this study are:
 - To find out if the TFV IVR is safe and well-tolerated when worn continuously for 91 days
 - To find out how the study drug TFV enters and exits the body when the IVR is inserted into the vagina and left in place for approximately 91 days.

- If you qualify and choose to participate, you will be asked to insert one of the two IVRs in your vagina and wear it continuously for approximately 91 days. You will be randomly assigned to one of two study groups (among 3 participants, 2 will be assigned to the TFV IVR group and 1 assigned to the placebo IVR group):
 - An IVR containing 1.4 g of TFV
 - A placebo IVR
- You will be asked to attend 10 clinic visits at this study clinic and will be followed for approximately 92 days. The total length of your participation in this study will be about four and a half months.
- At some of the clinic visits, the following will occur (other things may happen that are not listed here but are in the detailed descriptions of the study procedures):
 - A physical and/or pelvic exam will be performed;
 - Blood will be obtained to test for HIV and/or other sexually transmitted infections (STI);
 - Urine will be collected to test for infections and (if applicable) pregnancy;
 - If your medical records confirm that you have had your uterus removed above the cervix or have had both ovaries removed, you will not have to have pregnancy testing performed.
 - Vaginal and rectal fluids will be collected for research purposes and to test for STIs (if applicable). At 4 visits, cervical tissue will also be collected;
 - You will be asked to complete several short interviews. You may also be selected to complete a longer interview at Visit 9.
- Some common risks or discomforts from the IVR and the use of TFV in other forms include: upset stomach, fatigue, dizziness, depression, headache, vaginal irritation and/or discharge, allergic reaction, and vaginal or cervical ulcers. One serious but rare adverse reaction reported with the use of VR is toxic shock syndrome caused by poisons (toxins) released by some types of *Staphylococcus aureus*, a common bacteria, though a causal relationship has not been established.
- You may not experience any direct benefit from participation in this study, but information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive HIV/STI risk reduction counseling, HIV, HSV and STI testing, physical and pelvic examinations, and routine laboratory testing.
- Taking part in this research project is voluntary. You don't have to participate and you can stop at any time.
- If you decide not to join this study: there are methods available to prevent sexually transmitted HIV, including condom use during sex and/or the use of daily oral Truvada® for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Study staff can provide you with additional information about PrEP and PEP if you are interested.

Please take time to read this entire form and ask questions before deciding whether to take part in this study. If you do decide to take part in the trial, you will sign your name on this form. A copy of this form will be offered to you. Signing this consent form does not

mean you will be able to join the study. You must first complete the screening tests and exams to see if you are eligible. It is important to know that your participation in this research is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

STUDY PRODUCT

The drug TFV is used in the treatment and prevention of HIV. TFV works by preventing HIV from making copies of itself, which stops the spread of HIV in the body. HIV is the virus that causes AIDS.

TFV, in combination with other drugs, has been studied as an oral tablet (e.g., Truvada®) and shown to be safe and effective in the treatment and prevention of HIV infection. TFV has also been studied as a vaginal gel and shown to be safe but not consistently effective in prevention of HIV infection, due in part to inconsistent use of the gel in these studies. Very little clinical data exists on the safety or effectiveness of TFV when it is delivered via IVR. However, early results suggest that the TFV IVR would be safe and may deliver enough drug to prevent the spread of HIV in people.

The study IVRs are made of flexible plastic and are supplied by CONRAD, a not-for-profit research organization.

STUDY GROUPS

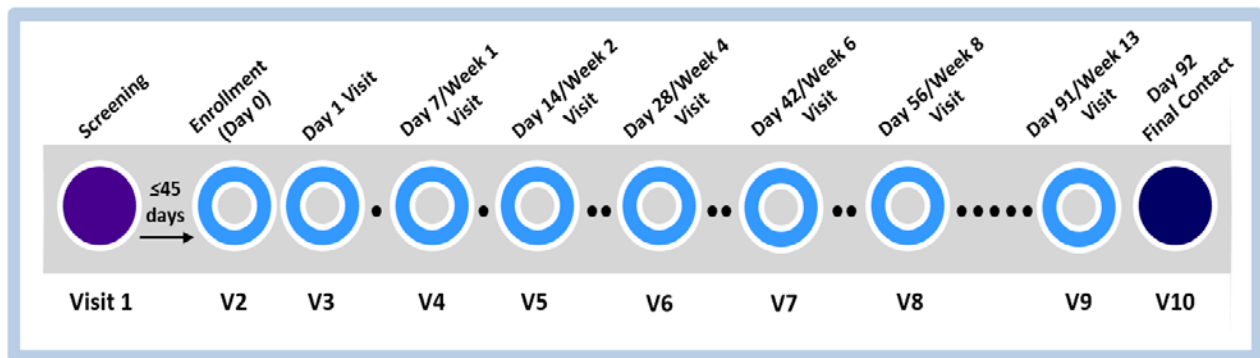
Approximately 48 eligible participants will be randomly assigned to one of two IVR study groups:

- A ring containing 1.4 g TFV, to be worn continuously for a total of 91 days
- A placebo ring that contains no drug or active ingredients, to be worn continuously for a total of 91 days

Approximately 32 participants will be assigned to use the TFV IVR, and approximately 16 participants will be assigned to the placebo IVR. Participants will be assigned to a group by random chance (like rolling dice). Neither you nor the study staff can control which group you will be assigned to.

WHAT WILL HAPPEN DURING THE STUDY VISITS?

The study includes a total of ten (10) clinic visits, including the Screening Visit today. All visits will take place at this clinic.



Screening Visit Procedures:

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

- Ask you questions to confirm that you are able to join the study.
- Ask you to provide study staff with your contact information (i.e., where you live and how we can get in touch with you).
- Ask you questions about your medical health (including what medications you are taking), menstrual history, and your understanding of the study requirements. They may also ask to view your medical records with your permission.
- Talk with you about the requirements of the study, including the importance of completing clinic visits and study activities and procedures according to the study schedule.
- Test your urine for pregnancy and, if needed, for infections.
 - If you are pregnant you cannot join this study.
 - Study staff will talk with you about ways to avoid becoming pregnant.
 - You will answer questions about whether you are using an effective method of contraception and intend to use this method for the entire time that you are in this study. Effective methods include:
 - Sterilization by you or your partner (tubal ligation, vasectomy, etc.).
 - Hormonal methods except contraceptive vaginal rings.
 - Intrauterine devices (IUDs) inserted at least 30 days before enrollment.
 - Having sex exclusively with individuals assigned female sex at birth.
 - Abstinence from penile-vaginal intercourse for 90 days before enrollment and planning to remain abstinent for the duration of study participation.
- Perform a physical examination.
- Perform a pelvic examination:
 - The study clinician will use a speculum (a plastic or metal instrument inserted in the vagina). Study staff will ask if you are experiencing symptoms of an infection. They will check your vagina and cervix for signs of infection and other problems.

- Collect a small amount of vaginal fluid via swab(s), like a Q-tip. These swabs will be used to test for sexually transmitted infections and diseases (commonly known as STIs or STDs) and other problems.
- If you are 21 years or older, the study staff may also collect samples from your cervix for a “Pap test” or “Pap smear”. Study staff will inform you of the results of your Pap test. It takes about **[SITES TO INSERT AMOUNT OF TIME]** before Pap test results are ready. If you are 21 years of age or older and have a written report confirming a normal Pap test in the past 3 years, or if you had an abnormal Pap test but had follow-up indicating no treatment was required, you will not need to have a Pap test taken at this screening visit. The results of your Pap test may affect whether you can join the study.
- Take a blood sample **[SITES TO INSERT AMOUNT]**:
 - To test the health of your blood, liver and kidneys.
 - To test for infections typically passed through sex, including HIV and Hepatitis B.
 - You will be told your test results as soon as they are available. You will talk with the study staff about the meaning of your results, how you feel about them, and learn about ways to prevent HIV and other STIs. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we are sure of your status. To participate in the study, you must receive the results of your HIV test. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.
- If needed, give you treatment or refer you for treatment of STIs or other urinary or reproductive tract infections.
- Inform you about other services, if needed.
- Provide you with the results of your tests, when available. It is expected that all your results will be available by **[SITES TO SPECIFY TIMEFRAME]**.
- Offer you male condoms, if you need them.
- Reimburse you for your visit.
- Schedule your next visit to enroll in the study, if you are willing and eligible.
 - Your menstrual cycle will be considered when scheduling your next visit because, ideally, no bleeding should occur on the first 7 days of product use.

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

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

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

<u>Activity:</u>	<u>For How Long?</u>
<ul style="list-style-type: none"> Receptive sexual practices, including: <ul style="list-style-type: none"> Penile-vaginal intercourse Penile-anal intercourse Receptive oral intercourse Finger stimulation 	<ul style="list-style-type: none"> For 72 hours before each clinic visit and for 72 hours after biopsy collection
<ul style="list-style-type: none"> Tampon use 	<ul style="list-style-type: none"> For 24 hours before each clinic visit
<ul style="list-style-type: none"> Inserting any objects into your vagina or rectum, including: <ul style="list-style-type: none"> Sex toys Female condoms Diaphragms Menstrual cups Cervical caps or any other vaginal barrier method 	<ul style="list-style-type: none"> For the duration of study participation, beginning 24 hours before the enrollment visit
<ul style="list-style-type: none"> Use of vaginal products, including: <ul style="list-style-type: none"> Spermicides Lubricants Contraceptive VRs Douches Vaginal medications Vaginal moisturizers 	<ul style="list-style-type: none"> For the duration of study participation, beginning 24 hours before the enrollment visit
<ul style="list-style-type: none"> Use of oral post-exposure or pre-exposure prophylaxis (PEP or PrEP) 	<ul style="list-style-type: none"> For the duration of study participation, beginning 3 months before the enrollment visit
<ul style="list-style-type: none"> Use of anticoagulants (e.g., heparin, Lovenox®, warfarin, Plavix® [clopidogrel bisulfate]) 	<ul style="list-style-type: none"> For the duration of study participation
<ul style="list-style-type: none"> Use of aspirin (greater than 81 mg) 	<ul style="list-style-type: none"> For 72 hours before and after a cervical biopsy collection visit

Enrollment and Follow-up Visit Procedures:

If you are found to be eligible, your next visit will be within 45 days of your Screening Visit today, and is called the Enrollment Visit. The procedures done during the Enrollment Visit will take about **[SITES TO INSERT TIME]**. This visit will take longer than most because we will collect a small amount of vaginal fluid over a period of 4 hours. At your Enrollment Visit, study staff will:

- Ask you questions to confirm you are able to join the study.
- Randomly assign you to one of two study groups. Participants in both study groups will have the same study visit schedule.
- Take blood samples **[SITES TO INSERT AMOUNT]**.
 - The blood samples will be collected:

- For HIV testing.
- For research purposes, to test for herpes simplex virus (HSV).
 - The HSV test results will not be available until the end of the study, and neither you nor study staff will know your HSV status until then. If you would like to receive your HSV test results after the end of the study, please let study staff know.
- In case there is a question about your lab results in the future.
- The same tests may be done when these samples are collected at future visits.
- Give you the study IVR to insert at the clinic. Study staff may help you insert the IVR if you cannot do it on your own. All participants will have an examination to ensure the ring is inserted correctly.
 - You will be asked to keep the IVR in place until the Day 91 study visit (Visit 9) and not remove it between visits. You will be given further instructions about what to do in the rare occasion the ring comes out or you need to remove it.
 - Study staff will show you how to take the ring out in case you need to.
 - Study staff will talk with you about what to do if you have any problems or symptoms while using the ring.
- Collect a small amount of vaginal fluid via swabs at two time points including at one and four hours after you insert the study IVR.
 - Collect swabs:
 - To measure the amount of TFV present in the vagina when using the study IVR and for other research purposes.
 - The same tests may be done when these samples are collected at future visits.

Follow-up study visits will take about **[SITES TO INSERT TIME]**. At most of these visits, including the Enrollment Visit, study staff will:

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

- You may use a computer to answer these questions. It is important that you know that you will answer these questions in private and your responses will be kept confidential.
- Talk with you about any problems or symptoms that you encounter as a result of wearing the IVR or undergoing any of the study procedures.
- Test your urine for pregnancy and, if needed, for infections.
- Take blood samples **[SITES TO INSERT AMOUNT]** to test your health and for research purposes, including to measure the amount of TFV present in your body when using the study IVR.
- Perform a targeted physical examination (including general appearance, temperature, heart rate and blood pressure) if needed.
- Perform a pelvic examination.
 - The study clinician will use a speculum to check your vagina and cervix for signs of problems due to the ring or infection. They may also collect vaginal fluid to test for infections and for research purposes.
 - At the Enrollment, Day 28 and Day 56 clinic visits (Visits 2, 6 and 8), the study clinician will perform a cervicovaginal lavage (CVL). For the CVL, a clinician rinses your vagina and cervix with a small amount of sterile fluid and collects that fluid in a tube for testing. The CVL fluid collected will be used for research purposes only.
 - At both the Day 14 and Day 56 clinic visits (Visits 5 and 8), or at both the Day 28 and Day 91 clinic visits (Visits 6 and 9), the study clinician will perform a cervical biopsy to collect tissue samples from your cervix. Which two visits you will be assigned to have the cervical biopsy will be selected randomly. At Visits 5 and 6, study clinicians will take approximately 2 small tissue samples from your cervix, each about the size of a grain of rice; at Visits 8 and 9, they will take approximately 4 small tissue samples from your cervix. These samples will be used to see how much of the study drug is in your tissue. It is important that you do not put anything in your vagina for 3 days before the biopsy tissue collections and 3 days after, which includes avoiding sexual intercourse, because you may be at higher risk for getting or spreading an infection until the biopsy sites have healed. It is also important that you do not take any aspirin doses higher than 81 mg per day for 3 days before and after the cervical biopsy tissue collections, because you may be at higher risk of bleeding.
- Take rectal fluid samples.
 - At the Day 1, Day 14, Day 28, Day 56 and Day 91 clinic visits (Visits 3, 5, 6, 8 and 9), the study clinician will use an anoscope (a short hollow tube inserted in your rectum) and insert swabs and sponges through the tube to collect rectal fluid for research purposes.
- Give you treatment or refer you for treatment for any issues they may find.
- Give you your test results, if available.
- Offer you condoms, if you need them.
- Reimburse you for your visit.

- Schedule your next visit, if applicable.

As with the Enrollment visit, your Day 91 study visit (Visit 9, when the study IVR is removed) will take longer than most because we will collect your blood and vaginal and rectal fluids over a period of 4 hours. This visit will take about **[SITES TO INSERT TIME]**. During this visit, study staff will:

- Take blood samples **[SITES TO INSERT AMOUNT]** right before you remove the study IVR and at four hours after you remove the study IVR. The blood samples will be collected:
 - For HIV testing.
 - To test the health of your blood, liver and kidneys, and for research purposes.
- Collect a small amount of vaginal fluid via swab and rectal fluid via anoscope at two time points including right before you remove the study IVR and at four hours after you remove the study IVR.
- Collect the study IVR from all participants.

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

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

Additional Visits and Procedures

It may be necessary for you to have additional visit(s) and/or provide additional samples if any of the above procedures need to be repeated due to one or more of the following:

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

Additional testing may be performed as part of quality control to ensure that the tests work correctly and supply accurate data.

In-depth Interview Subset:

You may be asked to participate in an interview with a trained staff member at your Day 91 clinic visit (Visit 9) to discuss your experiences during study participation. A total of approximately 24 participants across 3 sites will be interviewed. If you are asked to participate in this interview, you will be asked questions about your use of the ring, your preferences and opinions, your experiences with using the ring during sex, any problems you may have had using the ring, and whether you used the vaginal ring or not. This interview may take approximately 45-60 minutes and may occur over video chat. The interviews will be audio-recorded to make sure to record your words exactly how you said them. The audio recording, notes, and analyses from these materials will be kept

confidential and will only use study numbers or fake names, and the hardware will be physically protected in a locked area. This means that no one other than the MTN-038 study team will have access to your responses. The information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-038 study team for the purposes of this research. ***[Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs:*** The audio recordings, notes, and transcripts from these materials will be kept for at least two years after the intravaginal ring is approved for marketing or two years after all developmental research on the intravaginal ring is stopped.]

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws

Whenever your blood is drawn, you may have:

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

Risks of Pelvic Exams

During pelvic exams and cervical and vaginal fluid collection, you may feel discomfort or pressure in your vagina, genital area and/or pelvis. You may also have vaginal bleeding or spotting, which should stop shortly after the examination.

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

Risks of Vaginal Rings

Based on side effects reported among participants in previous IVR studies, vaginal rings may be associated with side effects listed below:

- Vaginal discharge
- Vaginal irritation or discomfort (including with vaginal intercourse)
- Itching of the vagina (vulvovaginal pruritus)
- Allergic reaction (including rash or other skin irritation, itching, joint pain, or difficulty breathing)

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

Risks of Tenofovir

The following side effects have been associated with the use of TFV in oral tablet form:

- Upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness
- Dizziness
- Depression
- Headache
- Abdominal pain
- Worsening or new kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas and liver. If you are developing liver problems, you may have one or more of the following symptoms:
 - Yellowing of the skin or whites of your eyes
 - Dark urine
 - Pain on the right side of your stomach
 - Loss of appetite, upset stomach or vomiting
 - Pale colored stools
 - Itchy skin
- Shortness of breath
- Rash
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Muscle pain and muscle weakness
- Elevated lactic acid levels in the blood and enlarged liver with fatty liver that may result in liver failure, other complications or death have been reported with the use of TFV and similar anti-HIV medications alone or in combination. The liver complications have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate elevated lactic acid levels in the blood include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness and shortness of breath.
- Sleeping problems

The following possible side effects have been associated with the use of TFV IVR:

- Headache
- Vulvovaginal pruritus
- Vulvovaginal pain
- Bladder discomfort
- Vaginal discharge
- Vaginal erythema

- Vaginal and cervical ulceration

Risks of Anoscope Rectal Exams

During collection of rectal fluid samples, insertion of a lubricated anoscope may cause mild discomfort or pressure in the rectum or anorectal area. There is a risk of mild discomfort in addition to a slight risk of bleeding with the insertion of rectal swabs or sponges.

Other Possible Risks

You may become embarrassed and/or worried when discussing your sexual practices, ways to protect against HIV and other STIs, and your test results. You may be worried while waiting for your test results. If you have HIV or other infections, learning this could make you worried. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. Reports via computer will be stored in computers that are password-protected and will not include personal information that could identify or link information to you; only your study ID number will be recorded.

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

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

Pregnancy and Breastfeeding

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

If you become pregnant at any time during the study, study staff will refer you to available medical care and other services you may need. The study does not pay for this care. You will not receive (or you will stop using) the study IVR and you will exit the study. The outcome of your pregnancy is important to study staff; therefore, your pregnancy will be followed until the results of your pregnancy are known. We may contact you to find out about the health of your pregnancy. If you become pregnant and you deliver a baby from that pregnancy, we will contact you approximately one year after your delivery to collect information about the health of your baby. **[SITE TO INCLUDE/AMEND THE FOLLOWING]**: We will also contact you about a study that collects information about pregnancy and babies up to one year old.

If You Become Infected with HIV

Your participation in this study will not cause HIV infection. The study drug does not cause HIV. However, there is always a chance that through sexual activity or other activities that you may become HIV-positive. In the unlikely event that you become HIV-positive, study staff will give you counseling and refer you for medical care and other available services. Tests may be performed to see if you have HIV drug resistance. This will allow doctors to know what HIV drugs would be best for the treatment of your type of HIV. If the HIV tests indicate you may be infected with HIV, you will stop using the IVR. If HIV infection is confirmed, you will stop your participation in this study.

BENEFITS

As mentioned previously, TFV has been shown to be safe and effective in preventing HIV when taken orally, but we do not yet know if it will prevent HIV when delivered via IVR. Though you may not experience any direct benefit from participation in this study, information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive HIV/STI risk reduction counseling, HIV, HSV and STI testing, physical examinations, pelvic examinations, and routine laboratory testing, including tests to check the overall health of your liver and kidneys.

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

If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. If you are diagnosed with a STI, you will receive medicine or a referral, if needed. You can bring your partner here for counseling and referral for testing and treatment for STIs, if needed.

NEW INFORMATION

You will be told of any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the IVR may be causing bad effects, you will be told about this. You will also be told

when the study results are available, and how to learn about them. Additionally, you will be told of any new information about other effective HIV-prevention products as they become available.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be removed from the study early without your permission if:

- The study is cancelled by the US FDA, US NIH, CONRAD (the nonprofit organization that supplies the IVRs), the US Office for Human Research Protections (OHRP), the MTN, the local government or international regulatory agency, or the Institutional Review Board (IRB). An IRB is a committee that watches over the safety and rights of research participants.
- The Study Monitoring Committee (SMC) recommends that the study be stopped early. The SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study.
- You are found to be infected with HIV.
- You become pregnant.
- Study staff decide that using the IVR would be harmful to you, for example, if you have a bad reaction to the study ring.
- Other reasons that may prevent you from completing the study successfully, such as inability to consistently keep appointments or to stop using prohibited medications or engaging in prohibited practices.

If study staff ask you to stop using the IVR, you will be asked to complete an interim visit during which time the procedures highlighted to occur at Visit 9 will be completed. Thereafter, you may continue your regular clinic visit schedule with modified procedures, unless otherwise informed by study staff.

If you are removed from or choose to leave this study, it will have no effect on the regular medical care that is available to you at this clinic or elsewhere. You will be asked to return your IVR and complete a final evaluation. If you do not have the IVR with you at the time of your contact with staff, staff members will make every effort to assist you in returning the ring as soon as possible. ***[SITE TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES]***

ALTERNATIVES TO PARTICIPATION

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

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

COSTS TO YOU

[SITE TO COMPLETE ACCORDING TO SITE CAPACITY]: There is no cost to you for study related visits, the IVR, physical/pelvic examinations, laboratory tests or other procedures. Treatments available to you from the study site for HIV/STIs may be given to you free of charge or you will be referred for available treatment for the duration of the study.

REIMBURSEMENT

[SITE TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT]: You will receive **[SITE TO INSERT AMOUNT \$XX]** for your time, effort, and travel to and from the clinic at each scheduled visit. If chosen to take part in the in-depth interview, you will receive **[SITE TO INSERT AMOUNT \$XX]**. You may receive **[SITE TO INSERT AMOUNT \$XX]** for any visits which occur in between your normally scheduled visits.

CONFIDENTIALITY

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

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

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US OHRP, NIH and/or contractors of NIH, and other local, US or international regulatory authorities.
- Representatives of CONRAD, including study monitors.
- Site IRBs or Ethics Committees.
- Study staff.

[SITE TO INCLUDE/AMEND THE FOLLOWING]:

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

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

RESEARCH-RELATED INJURY

[SITE TO SPECIFY INSTITUTIONAL POLICY]: It is unlikely that you will be injured as a result of study participation. If you are injured, the ***[INSTITUTION]*** will give you immediate necessary treatment for your injuries. You ***[WILL/WILL NOT]*** have to pay for this treatment. You will be told where you can receive additional treatment for your injuries. The U.S. NIH does not have a mechanism to pay money or give other forms of compensation for research related injuries. You do not give up any legal rights by signing this consent form.

CLINICALTRIALS.GOV

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

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

[SITE TO SPECIFY INSTITUTIONAL POLICY]: Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic.

PROBLEMS OR QUESTIONS

If you ever have any questions about the study, or if you have a research-related injury, you should contact ***[INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]*** at ***[INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS]***.

If you have questions about your rights as a research participant, you should contact ***[INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]*** at ***[INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER]***.

CONSENT FOR LONG-TERM STORAGE AND FUTURE TESTING OF SPECIMENS

There might be a small amount of blood, tissue, rectal or vaginal fluid left over after we have done all the study related testing. We would like to ask your permission to store these leftover samples and related health information for use in future studies, such as future research to fight HIV and other related diseases. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range. If you agree, your samples and related health data will be stored safely and securely at facilities that are designed so that only approved researchers will have access to the samples. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you.

You can still enroll in this study if you decide not to have leftover samples stored for future studies. If you do not want the leftover samples stored, we will destroy them.

The type of testing planned for your leftover specimens is not yet known. However, samples may be used by the MTN Laboratory Center to complete additional quality assurance testing, ensuring that the tests work correctly and supply accurate data. No genetic testing on either a limited set or the full set of genes is planned for leftover specimens that are stored for the purposes of future research. It is important that you know that any future testing or studies planned for these specimens must be approved by an Institutional Review Board before they can be done.

You can withdraw your consent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study. However, researchers will not be able to destroy samples or information from research that is already underway.

Initials and Date

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

Initials and Date

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

SIGNATURES- VOLUNTARY CONSENT

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC]: If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to the study, please sign your name or make your mark below.

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