MTN-039

A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels

Microbicide Trials Network

Funding Agencies:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine transaminase
API	active pharmaceutical ingredient
ARV	antiretroviral drugs
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under the curve extrapolated to infinity
AUC_{last}	area under the curve up to the last measurable concentration
BID	bis in die, or twice per day
BPA	bisphenol A
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
BV	bacterial vaginosis
CASI	computer assisted self-interview
CBC	complete blood count
CD4	cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
cDNA	complementary DNA
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	maximum concentration
CMRB	Clinical Microbicide Research Branch
CNS	central nervous system
COBI	cobicistat
CRF	case report form
CRMS	Clinical Research Management System
CRS	Clinical Research Site
CT	*Chlamydia trachomatis,* Chlamydia
CTA	Clinical Trial Agreement
CVF	cervicovaginal fluid
CWG	Community Working Group
CYP1A2	cytochrome P450 family 1, subfamily A2 genetic locus
CYP2C8	cytochrome P450 family 2, subfamily C8 genetic locus
CYP2C9	cytochrome P450 family 2, subfamily C9 genetic locus
CYP2C19	cytochrome P450 family 2, subfamily C19 genetic locus
CYP2D6	cytochrome P450 family 2, subfamily D6 genetic locus
CYP2E1	cytochrome P450 family 2, subfamily E1 genetic locus
CYP3A	cytochrome P450, family 3, subfamily A genetic locus
CYP3A4	cytochrome P450 family 3, subfamily A4 genetic locus
CYP450	cytochrome P450

DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DAIDS PRO	DAIDS Protocol Registration Office
DAPY	di-amino-pyrimidine
DLV	delavirdine
DNA	deoxyribonucleic acid
DOD	directly observed dosing
EAE	expedited adverse event
EC	ethics committees
EC_{50}	50% effective concentration
EFV	efavirenz
ENR	enrollment
EU	European Union
EVG	elvitegravir
FDA	(US) Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
FMO	flavin-containing monooxygenase
FTC	emtricitabine
g	grams
GC	*Neisseria gonorrhoeae,* gonorrhea
GCP	Good Clinical Practices
GEE	generalized estimating equations
GMP	Good Manufacturing Practices
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HEC	hydroxyethylcellulose
HEENT	Head, Eye, Ear, Nose and Throat Examination
HHS	(U.S.) Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus type 1
HIV-1 IIIB	Human Immunodeficiency Virus type 1, IIIB strain
HPTN	HIV Prevention Trials Network
HPV	human papillomavirus
HSV	herpes simplex virus
HSV-1/2	herpes simplex virus type 1/2
hu-PBL	human peripheral blood lymphocytes
hu-SCID	humanized severe combined immunodeficient
IATA	International Air Transport Association
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IDI	In-Depth Interview
IL	Interleukin
IND	Investigational New Drug
INR	International normalized ratio
INSTI	Integrase strand transfer inhibitor

IoR	Investigator of Record
IRB	Institutional Review Board
IUD	intrauterine device
kg	kilogram
LC	Laboratory Center
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantification
LOC	Leadership and Operations Center
µg	microgram
MDP	Microbicides Development Programme
mg	milligram
mL	milliliter
mM	millimolar
MO	Medical Officer
mOsm	milliosmole
MPA	medroxyprogesterone acetate
mRNA	mitochondrial ribonucleic acid
MT-2	human melatonin receptor 2
MTN	Microbicide Trials Network
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole
n	number
N-9	nonoxynol-9
NAAT	nucleic acid amplification test
NF	National Formulary
ng	nanogram
nM	nanomolar
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NL	network laboratory
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleotide analogue reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NS	normal saline
NSAIDS	non-steroidal anti-inflammatory drugs
NVP	nevirapine
OHRP	Office for Human Research Protections
P24	protein 24
PBL	peripheral blood lymphocytes
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PD	pharmacodynamics
PEP	post-exposure prophylaxis
pH	potential of hydrogen
PI	protease inhibitors
PID	pelvic inflammatory disease
PK	pharmacokinetics

PMPA	9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development, Inc.
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PSP	Prevention Sciences Program
PSRT	Protocol Safety Review Team
PSS	polystyrene sulfonate
PT	prothrombin time
PTID	participant identification
PVC	polyvinyl chloride
QD	quaque die, or once per day
RAI	receptive anal intercourse
RE	Regulatory Entity
RF	rectal fluid
RG	reduced-glycerin
RNA	ribonucleic acid
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
RT-PCR	real-time polymerase chain reaction
Rx	treatment
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SCID	severe combined immunodeficient
SCR	screening
SDMC	Statistical Data Management Center
SHIV	simian human immunodeficiency virus
SMC	Study Monitoring Committee
SOP	standard operating procedure
SMS	short message service
SSP	study specific procedures
STI	sexually transmitted infection
SubQ	subcutaneous
SUSAR	suspected, unexpected serious adverse reaction
TAF	tenofovir alafenamide
TCID	tissue culture infective dose
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TEAE	treatment emergent adverse event
$T_{1/2}$	half-life
T_{max}	time at which C_{max} is observed
TPGS	tocopheryl polyethylene glycol succinate
TV	trichomonas vaginalis
UA	urinalysis
ULN	upper limit of normal
UPMC	University of Pittsburgh Medical Center
USA	United States of America

USP	United States Pharmacopoeia
UTI	urinary tract infection
WHO	World Health Organization
w/w	weight/weight

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MTN-039

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INVESTIGATOR SIGNATURE FORM
Version 1.0; March 6, 2019

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: 38470)

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 Date

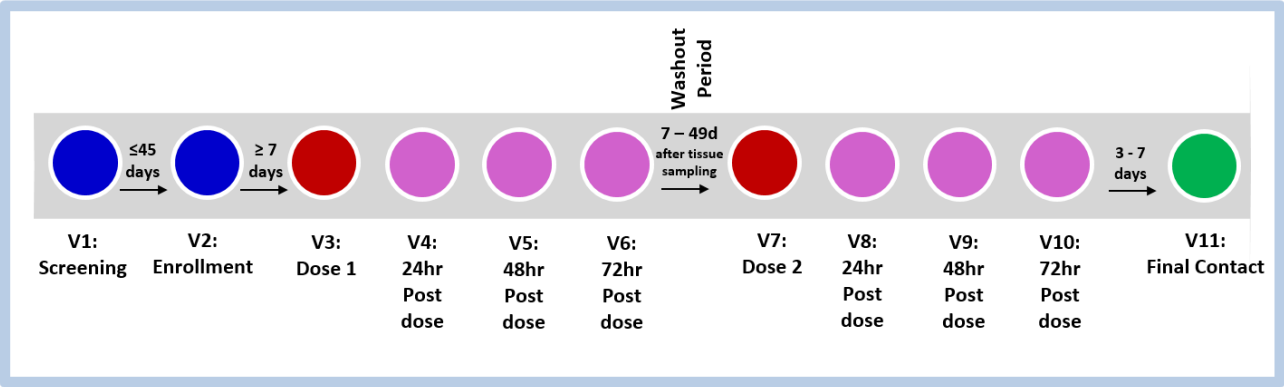
MTN-039

A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels

PROTOCOL SUMMARY

Short Title:	Safety and PK Study of TAF/EVG Administered Rectally
Clinical Phase:	Phase 1
IND Sponsor:	DAIDS
Protocol Chair:	Sharon Riddler, MD, MPH
Sample Size:	MTN-039 will enroll approximately 20 participants.
Study Population:	HIV-uninfected individuals 18 years of age or older
Study Sites:	Sites selected by MTN Executive Committee
Study Design:	Phase 1, multi-site, open-label, single arm, two-period study of rectal administration of one Tenofovir Alafenamide/Elvitegravir Insert, 20/16 mg and then two TAF/EVG Inserts
Study Duration:	Approximately 6-13 weeks of follow-up per participant is planned with a projected accrual period of 6-8 months. The total duration of the study will be approximately 11 months.
Study Products:	TAF/EVG Insert, 20/16 mg
Study Regimen:	Participants will apply a single TAF/EVG Insert rectally and samples will be collected over a 3-day period. After a washout period of at least 7 days, participants will apply two TAF/EVG Inserts rectally and samples will be taken over a 3-day period.

Figure 1: MTN-039 Study Visit Schedule



Primary Objectives:

Safety

- To evaluate the safety of the TAF/EVG Insert, 20/16 mg administered rectally at two dose levels: 1 insert and 2 inserts

Pharmacokinetics

- To characterize the systemic and rectal pharmacokinetics of the TAF/EVG Insert, 20/16 mg applied rectally at two dose levels: 1 insert and 2 inserts

Primary Endpoints:

Safety

- All Grade 2 and higher AEs

Pharmacokinetics

- EVG concentrations in:
  - Blood
  - Rectal fluid
  - Rectal mucosal tissue homogenates

- TAF and TFV concentrations in
  - Blood
  - Rectal fluid

- TFV-DP concentration in:
  - Rectal mucosal tissue homogenates
  - Rectal mucosal tissue cell isolates

Secondary Objective:

Acceptability

- To identify product attributes considered likely to challenge and/or facilitate future sustained use of the TAF/EVG Insert applied rectally

Secondary Endpoints:

Acceptability

- Participant report of overall acceptability of the TAF/EVG Insert applied rectally

Exploratory Objectives:

***Ex Vivo* Efficacy**

- To assess the preliminary (*ex vivo)* efficacy of TAF/EVG after product is inserted rectally

Pharmacokinetics

- To characterize the cervicovaginal pharmacokinetics of the TAF/EVG Insert, 20/16 mg applied rectally at two dose levels: 1 insert and 2 inserts

Mucosal Safety

- To evaluate mucosal safety of the TAF/EVG Insert, 20/16 mg applied rectally at two dose levels: 1 insert and 2 inserts

Exploratory Endpoints:

***Ex Vivo* Efficacy**

- Changes in HIV-1 replication in colorectal explant culture supernatant
- Anti-HIV activity in rectal fluid
- Anti-HIV activity in cervicovaginal fluid

Pharmacokinetics

- EVG, TAF and TFV concentrations in cervicovaginal fluid

Mucosal Safety

- Rectal histology
- Rectal proteomics
- Rectal metabolomics
- Rectal immunophenotype
- Rectal microbiome
- Cervicovaginal microflora

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels
Protocol Number:	MTN-039
Short Title:	Safety and PK Study of TAF/EVG Administered Rectally
Date:	March 6, 2019

1.2 Funding Agencies, Sponsor and Monitor Identification

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IND Sponsor:	US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH) 5601 Fishers Lane Rockville, MD 20852 USA
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2 INTRODUCTION

2.1 Background of Rectal Microbicide Research and Study Rationale

Microbicides are products that are designed to be applied to the vaginal or rectal mucosa with the intent of preventing the acquisition of sexually transmitted infections (STIs) including the human immunodeficiency virus (HIV).[1] While the original impetus for vaginal microbicide development was to provide women with options for HIV prevention in settings where their partners were unwilling to use condoms for penile-vaginal intercourse, there is recognition that rectal microbicides are needed for men and women who practice receptive anal intercourse (RAI).

RAI is associated with the highest probability for sexual acquisition of HIV infection. Unprotected RAI is the sexual behavior with the highest per act risk of HIV acquisition conferring approximately 10 to 20 times more risk than unprotected receptive vaginal intercourse.[2,3] Globally, transgender females and men who have sex with men (MSM) are 19 times more likely to be living with HIV compared with the general population.[4,5]

Elvitegravir (EVG) is a human immunodeficiency virus-1 (HIV-1) integrase inhibitor that has shown potent activity against laboratory viral strains and clinical isolates of HIV-1 and against virus with resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Elvitegravir is FDA approved and currently available in single tablet combination formulations for the treatment of HIV-1 infection.

Tenofovir alafenamide (TAF: formally known as GS-7340) is a prodrug of the antiviral acyclic nucleoside phosphonate tenofovir (TFV) with improved properties relative to tenofovir disoproxil fumarate (TDF). By enhancing stability in biological matrices while being rapidly activated in cells, TAF produces higher levels of intracellular TFV diphosphate, the pharmacologically active metabolite, in HIV-target cells at substantially reduced oral dose of TFV equivalents. It has been shown to have improved renal function and possibly reduced bone impairment compared to TDF.[6] TAF is US Food and Drug Administration (FDA) approved and currently available as a single tablet formulation for the treatment of chronic hepatitis B (Vemlidy®) and also co-formulated with other drugs for the treatment of HIV infection (Genvoya®, Odefsey® and Descovy®).

MTN-039 will evaluate the safety and pharmacokinetics (PK) of the TAF/EVG Insert administered rectally at two dose levels. Fast-dissolve topical inserts are an on-demand dosage form that is economical, discreet, user-friendly and user-initiated, factors that may encourage use in populations at risk for HIV acquisition.

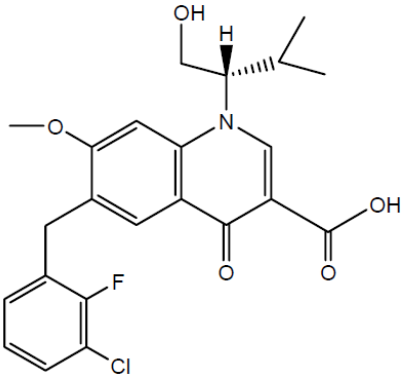
2.2 Elvitegravir (EVG) – Description and Mechanism of Action

2.2.1 Description

Elvitegravir (EVG) drug substance is a 2nd generation human immunodeficiency virus (HIV) integrase inhibitor. EVG is a white crystalline irregularly shaped material and has an acidic pKa of 6.6 and Log D of 4.5 at pH 6.8. EVG is a poorly water soluble and highly

permeable drug. It is considered a BCS class-2 compound. EVG (anhydrous crystalline form γ) is chemically stable in the solid state when exposed to heat, humidity and light.

The chemical name of EVG is (S)-6-(3-chloro-2-fluorobenzyl)-1-(1-hydroxy-3-methylbutan-2-yl)-7methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid. It has a molecular formula of $C_{23}H_{23}ClFNO_5$ and a molecular weight of 447.9 (free acid). It has the following structural formula:



EVG is a white to off-white crystalline powder with a solubility of > 35µg/mL in aqueous buffers at pH 9.0. EVG is stable for at least three years at 30°C.

2.2.2 Mechanism of action

EVG is an HIV-1 integrase strand transfer inhibitor (INSTI). Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection. EVG does not inhibit human topoisomerases I or II.[7]

2.2.3 Strength of Study Product

The doses of EVG proposed for use in MTN-039 are 16 mg in one insert and 32 mg in two inserts.

2.3 Non-Clinical Studies of Elvitegravir

2.3.1 *In Vitro* Studies

2.3.1.1 Anti-HIV-1 Activity

The antiviral activity of EVG against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cells, monocyte/macrophage cells, and primary peripheral blood lymphocytes. The 50% effective concentration (EC_{50}) values ranged from 0.02 to 1.7 nM. EVG displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.1 to 1.3 nM) and activity against HIV-2 (EC_{50} value of 0.53 nM). The antiviral activity of EVG with antiretroviral drugs in two-drug combination studies was not antagonistic when combined with the INSTI raltegravir, NNRTIs (efavirenz, etravirine, or nevirapine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine), PIs (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir), the fusion inhibitor

enfuvirtide, or the CCR5 co-receptor antagonist maraviroc. EVG did not show inhibition of replication of HBV or HCV in cell culture.[7]

The antiviral activity of EVG drug substance prepared at varying doses in suspension with insert formulation components was tested in a cervicovaginal tissue explant model. Complete protection against HIV-1_{BAL} infection was observed when EVG tissue concentrations were in the range of ~10^3-10^4 ng/g, whereas only partial protection was observed at ~10^2 ng/g. These data suggest that EVG tissue concentration of at least 1000 ng/g will be efficacious prophylactically against HIV infection of cervicovaginal tissue and therefore were set as the target benchmark for drug development.[8]

2.3.1.2 Resistance (HIV)

HIV-1 isolates with reduced susceptibility to EVG were selected in cell culture. Reduced susceptibility to EVG was associated with the primary integrase substitutions T66A/I, E92G/Q, S147G, and Q148R. Additional integrase substitutions observed in cell culture selection included D10E, S17N, H51Y, F121Y, S153F/Y, E157Q, D232N, R263K, and V281M.[7]

2.3.1.3 Cross-resistance (HIV)

EVG-resistant viruses showed varying degrees of cross-resistance in cell culture to raltegravir in the INSTI class depending on the type and number of substitutions in HIV-1 integrase.[7]

2.3.1.4 Mutagenicity and Carcinogenesis

EVG was not genotoxic in the reverse mutation bacterial test (Ames test) and the rat micronucleus assay. In an in vitro chromosomal aberration test, EVG was negative with metabolic activation; however, an equivocal response was observed without activation.[7]

2.3.1.5 *In Vitro* Metabolism

The metabolism of EVG is mediated primarily via intestinal and hepatic cytochrome P450 (CYP) 3A enzymes.[7]

2.3.1.6 *In Vitro* Dissolution (EVG insert)

An EVG insert offers rapid dissolution: an *in vitro* 96% dissolution is achieved within 15 minutes (see Table 1).[9]

Table 1: *In vitro* Dissolution of 8 mg Elvitegravir Insert

Time (min)	Average (% release) N=3	%RSD N=3
5	44.9	4.5
10	76.1	3.9
15	95.7	2.0
30	99.9	1.1
45	100.1	1.0
60	100.1	0.9

RSD – relative standard deviation

2.3.2 Animal Studies

2.3.2.1 Pharmacokinetics

Oral EVG

EVG displays modest bioavailability following oral administration in rats and dogs of 34.1% and 29.6%, respectively, and systemic clearance values of 0.5 L/h/kg and 1.0 L/h/kg, respectively, representing low to intermediate values relative to hepatic blood flow in these species (3.5 and 2.6 L/h/kg, respectively). Maximum plasma concentrations (Cmax) were achieved in 0.5–1.0 hour post-dose and terminal t½ (t½b) values were 2.3 and 5.2 hours, respectively.[10]

EVG/TDF Insert – Macaque Study

A dose-ranging PK study of EVG-containing inserts administered vaginally to female pigtail macaques was conducted by CONRAD (see Table 2 for study design). Vaginal inserts containing a combination of 2.7 mg or 8 mg elvitegravir/tenofovir disoproxil fumarate (EVG/TDF) were administered to female pigtailed macaques to assess systemic and local pharmacokinetics (PK). Blood, vaginal and rectal fluid, and/or vaginal tissue biopsy samples were collected at baseline, 0.5, 2, 6, and 24 hours, and 7 and 8 days following once weekly dosing for 4 weeks. Following a single dose of 8mg EVG/TDF, samples were also collected at 3 and 7 days post-dose to assess the PK tail. The samples were analyzed for concentrations of EVG. Study results can be found in the IB of the EVG insert.[8]

Table 2: Study design of the pharmacokinetic study of EVG/TDF vaginal inserts in pigtailed macaques

Group	Treatment	Week(s) Dosed	Number of Animals
PK (2-24 hours)			
1A	2.7mg EVG/TDF	1-4	3
2A	2.7mg EVG/TDF	1-4	3
1B	8mg EVG/TDF	1-4	3
2B	8mg EVG/TDF	1-4	3
PK Tail			
1A, 1B, 2A, and 2B	8mg EVG/TDF	1	12

Note: The same animals used for the PK assessment were also used in the PK Tail assessment, following a 2 week rest period.

EVG Insert – Vaginal Irritation Study of EVG in Rabbits

Twenty-four rabbits were involved in CONRAD Study 1645-113, a vaginal irritation study of EVG to evaluate potential local irritation and determine the pharmacokinetics following once daily intravaginal administration of EVG in New Zealand White Hra:(NZW) SPF rabbits for 14 consecutive days – group assignments are shown in Table 3.[11]The samples

were analyzed for concentrations of EVG. Study results can be found in the IB of the EVG insert.[8]

Table 3: Group Assignments in EVG Vaginal and Rectal Irritation Studies

Group Number	Treatment	Dose Level	Number of Animals in Vaginal Irritation study	Number of Animals in Rectal Irritation study	
				Male	Female
1	Reference Control (N-9)	4%	4	4	4
2	Vehicle Control (PBS+5% glycerin)	0 mg	4	4	4
3	Placebo Control	0 mg	4	4	4
4	1X EVG *	2 mg	4	4	4
5	3X EVG **	6 mg	4	4	4
6	10X EVG **	20 mg	4	4	4

N-9 = 4% nonoxynol-9; PBS= phosphate buffered saline
* 1X EVG (8 mg active drug/4 mL vehicle) was prepared from ground elvitegravir insert powder formulated in PBS and glycerin
** 3X EVG (24 mg active drug/4 mL vehicle) and 10X EVG (80 mg active drug/4 mL vehicle) was prepared from ground placebo insert powder and elvitegravir drug substance formulated in PBS and glycerin
For vaginal irritation study: Dose route was intravaginal for all animals; volume = 1 mL
For rectal irritation study: Dose route was rectal for all animals; volume = 1 mL

EVG Insert – Rectal Irritation Study of EVG in Rabbits

Forty-eight rabbits were involved in CONRAD Study 1645-114, a rectal irritation study of EVG to evaluate potential local irritation and determine the pharmacokinetics following once daily intrarectal administration of EVG in New Zealand White Hra:(NZW) SPF rabbits for 14 consecutive days. Group assignments are shown in Table 3. Pharmacokinetic study findings can be found in the IB of the EVG insert.[8]

2.3.2.2 Toxicology

EVG Insert – Vaginal Irritation Study of EVG in Rabbits

CONRAD Study 1645-113 assessed PK and potential for local irritation following once daily intravaginal administration of EVG in New Zealand White Hra:(NZW) SPF rabbits for 14 consecutive days. The assessment of toxicity in this study was made based on mortality, clinical observations, body weights, vaginal irritation scoring examinations, and anatomic pathology. There were no test article-related effects or definitive control article-related effects observed for these parameters.[8]

EVG Insert – Rectal Irritation Study of EVG in Rabbits

CONRAD Study 1645-114 assessed PK and potential for local irritation following once daily intrarectal administration of EVG in New Zealand White Hra:(NZW) SPF rabbits for 14 consecutive days. The assessment of toxicity in this study was made based on mortality, clinical observations, body weights, and macroscopic and microscopic

pathology of the rectum and surrounding tissues. There were no test article-related effects or definitive control article-related effects observed for these parameters.[8]

2.3.2.3 Mutagenicity and Carcinogenesis

EVG was not genotoxic in the rat micronucleus assay. Long-term carcinogenicity studies of oral EVG were carried out in mice (104 weeks) and in rats (up to 88 weeks in males and 90 weeks in females). No drug-related increases in tumor incidence were found in mice at doses up to 2000 mg per kg per day alone or in combination with 25 mg per kg per day ritonavir at exposures 3- and 14-fold, respectively, the human systemic exposure at the recommended daily dose of 150 mg. No drug-related increases in tumor incidence were found in rats at doses up to 2000 mg per kg per day at exposures 12- to 27-fold, respectively, in male and female, the human systemic exposure.[7]

2.3.2.4 Pregnancy, Teratogenic Effects, and Lactation

Oral EVG studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with EVG during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures (AUC) at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 23 and 0.2 times higher than the exposure in humans at the recommended daily dose of 150 mg.[7]

Studies in rats have demonstrated that EVG is secreted in milk.[7]

2.3.2.5 Reproductive Toxicity

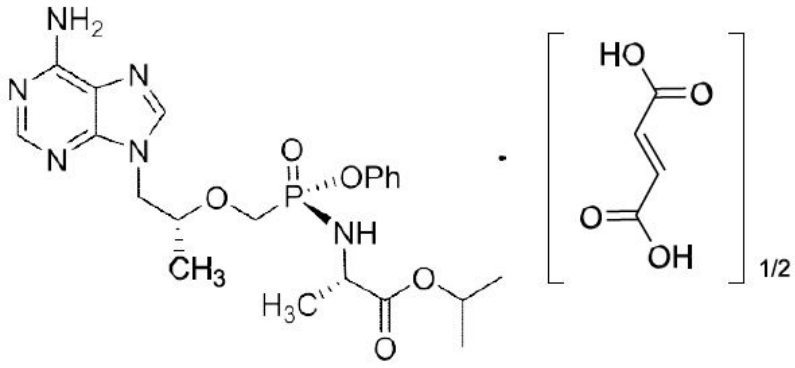
Oral EVG did not affect fertility in male and female rats at approximately 16- and 30-fold higher exposures (AUC), respectively, than in humans at the therapeutic 150 mg daily dose. Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 18-fold higher than human exposures at the recommended 150 mg daily dose.[7]

2.4 Tenofovir Alafenamide (TAF) – Description and Mechanism of Action

2.4.1 Description

Tenofovir alafenamide (TAF) is a nucleotide reverse transcriptase inhibitor and a prodrug of tenofovir. TAF is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.[12]

The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1). It has an empirical formula of C21H29O5N6P•½(C4H4O4) and a formula weight of 534.50. It has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.[12]

2.4.2 Mechanism of action

TAF is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate (TFV-DP). TFV-DP inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

TFV has activity that is specific to human immunodeficiency virus and hepatitis B virus. Cell culture studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined in cells. TFV-DP is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity in cell culture based on several assays including mitochondrial DNA analyses.[13]

2.4.3 Strength of Study Product

The doses of TAF proposed for use in MTN-039 are 20 mg in 1 insert and 40 mg in 2 inserts.

2.5 Non-Clinical Studies of Tenofovir Alafenamide

2.5.1 *In Vitro* Studies

2.5.1.1 Anti-HIV-1 Activity

The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), primary monocyte/macrophage cells and CD4-T lymphocytes. The EC50 values for TAF ranged from 2.0 to 14.7 nM. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC50 values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC50 values ranged from 0.91 to 2.63 nM).[13]

2.5.1.2 Resistance (HIV)

HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.[13]

2.5.1.3 Cross-resistance (HIV)

TFV resistance substitutions, K65R and K70E, result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. HIV-1 with multiple TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R, showed reduced susceptibility to TAF in cell culture.[13]

2.5.1.4 *In Vitro* Metabolism

TAF is reportedly hydrolyzed within cells to form TFV, which is phosphorylated to the active metabolite, TFV-DP. *In vitro,* TAF is reportedly metabolized to TFV by carboxylestrase 1 in hepatocytes, by cathepsin A in PBMCs and macrophages, with minimal metabolism via CYP3A.[14]

2.5.2 Animal Studies

2.5.2.1 Pharmacokinetics

Oral TAF – Dog Studies

The hepatic delivery and metabolism of TAF in primary human hepatocytes in vitro and in dogs in vivo were evaluated in one study. Incubation of primary human hepatocytes with TAF resulted in high levels of the pharmacologically active metabolite TFV-DP, which persisted in the cell with a half-life of >24 h. Following oral administration of TAF to dogs for 7 days, TAF was rapidly absorbed. The appearance of the major metabolite TFV in plasma was accompanied by a rapid decline in circulating TAF. Consistent with the in vitro data, high and persistent levels of TFV-DP were observed in dog livers. Notably, higher liver TFV-DP levels were observed after administration of TAF than those given TDF.[15]

To understand how TAF reduces first-pass clearance to be an effective oral prodrug, its permeability and stability were characterized *in vitro* and detailed pharmacokinetic studies were completed in dogs. TAF showed concentration-dependent permeability through monolayers of caco-2 cells and dose-dependent oral bioavailability in dogs, increasing from 1.7% at 2 mg/kg to 24.7% at 20 mg/kg, suggesting saturable intestinal efflux transport. Consistent with the proposed role of intestinal efflux transport, coadministration of low dose GS-7340 with a transport inhibitor substantially increased GS-7340 exposure. The result of effective oral absorption and efficient lymphoid cell loading was reflected in the high and persistent levels of the pharmacologically active metabolite, TFV

diphosphate, in peripheral blood mononuclear cells following oral administration to dogs.[16]

2.5.2.2 Mutagenicity, Carcinogenesis and Impairment of Fertility

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice is observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of TDF for HIV-1 infection. The TFV exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of Genvoya treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures 10 times (300 mg TDF) and 167 times (10 mg TAF in Genvoya) that in humans. In rats, the study was negative for carcinogenic findings.[13]

TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.[13]

2.5.2.3 Toxicology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three and nine month administration of TAF; reversibility was seen after a three month recovery period. At the NOAEL for eye toxicity, the systemic exposure in dogs was 5 (TAF) and 15 (TFV) times the exposure seen in humans at the recommended daily Genvoya dosage.[13]

2.6 Non-Clinical Studies of Elvitegravir and Tenofovir Alafenamide

2.6.1 *In Vitro* Studies

2.6.1.1 *In Vitro* Dissolution (TAF/EVG Insert)

A test of the in vitro dissolution of the TAF/EVG Insert was completed and the dissolution rate is listed in Table 4.

Table 4: *In vitro* Dissolution of 20/16 mg TAF/EVG Insert

Time (min)	TAF		EVG	
	Average (% release) *N=6*	**%RSD N=6**	**Average (% release) *N=6***	**%RSD N=6**
5	20	9.5	18	11.3
10	41	10.3	38	11.2
15	59	9.9	57	10.4
30	90	5.3	87	5.3
45	97	1.7	95	1.5
60	97	1.6	95	1.5
75	97	1.6	96	1.4

RSD – relative standard deviation

2.6.2 Animal Studies

2.6.2.1 Pharmacokinetics

TAF + EVG Solution – Mice Study

A pharmacokinetic and tissue distribution study of drug-loaded nanoparticle (NP) was performed in female humanized $CD34^{+}$-NSG mice to explore if a long-acting parenteral formulation of AVR may be an effective alternative to daily oral dosing. Mice received 200 mg/kg each of TAF and EVG as free drugs (TAF + EVG solution) or as drug loaded NP (TAF + EVG NP) formulation by subcutaneous (SubQ) administration. Plasma and tissue were collected to determine tenofovir (TFV) and EVG concentrations using LC-MS/MS. SubQ administration of TAF + EVG NP formulation resulted in long residence time and exposure for both drugs. The $AUC_{(0\text{-}72h)}$ of TFV and EVG was 14.1 ± 2.0, 7.2 ± 1.8 µg × hr./mL from free drugs in solution and the $AUC_{(0\text{-}14day)}$ for the same drugs was 23.1 ± 4.4, 39.7 ± 6.7 µg × hr./mL from NPs. The observed elimination half-life ($t_{1/2}$) for TFV of free and NPs were 14.2 h, 5.1 days and for EVG 10.8 h, 3.3 days, respectively.[17]

TAF/EVG Insert – Macaque Study

CONRAD study 2708 evaluated the PK of TAF and EVG following administration of vaginal inserts containing a combination of TAF/EVG in female pigtailed macaques. Vaginal inserts containing 10/8 mg, 10/16 mg or 40/24 mg of TAF/EVG were administered to groups of 4 female macaques. One insert was administered vaginally to each macaque 5 times over an 8-week period with at least 1 week between doses. Animals were dosed on a single occasion at the 24h PK interval and on two separate occasions for both 2 and 4h PK intervals. Plasma, vaginal fluid and vaginal tissue biopsy samples were collected at 0.5 (blood only), 2, 4 and 24 hours post-dose. These samples were analyzed for concentrations of TAF, TFV and EVG. Vaginal biopsies were also evaluated for TFV-DP concentrations. The TAF/EVG insert did not result in adverse behavioral changes, physical changes in the vaginal vault or measurable systemic exposure to TAF, TFV or EVG in the macaques.[14] There was minimal dose proportionality between inserts for vaginal fluid or tissue concentrations. TFV and EVG in vaginal fluid after administration

of TAF/EVG (20/16 mg) showed the most favorable PK and resulted in TFV-DP and EVG tissue levels in range with those shown to provide in vivo protection against vaginal SHIV infection in macaques.[18]

TAF/EVG Insert – Vaginal Irritation Study of EVG/TAF in Rabbits

CONRAD Study 1645-116 evaluated the PK of TAF/EVG following once daily intravaginal administration of TAF/EVG formulated drug substance in female NZW SPF rabbits for 14 consecutive days. 5/4, 15/12 or 25/20 mg TAF/EVG formulated drug substance were administered to 5 groups of 4 female rabbits. The bioanalytical and PK assessments are summarized below.

Median peak EVG plasma concentrations were observed by 0.5 to 1 hour postdose on Days 1 and 13. Mean C_{max} values, ranging from 17.5 to 49.4 ng/mL, for EVG appeared to increase with increasing dose across the dose range on Days 1 and 13. Mean $AUC_{0\text{-}24hr}$ values appeared to increase with increasing dose across the dose range on Day 1 and did not appear to increase with increasing dose on Day 13. Systemic exposure ($AUC_{0\text{-}24hr}$) to EVG did not appear to consistently change following repeated administration. Following the highest dose administered vaginally (25/20 mg TAF/EVG), mean EVG $AUC_{0\text{-}24hr}$ was 441 hr*ng/ml on Day 1 and 366 hr*ng/ml on Day 13.

Median peak TFV plasma concentrations were observed by 0.5 and 1 hour postdose on Days 1 and 13. Mean C_{max} values, ranging from 41.0 to 354 ng/mL, for TFV appeared to increase with increasing dose across the dose range on Days 1 and 13. Mean $AUC_{0\text{-}24hr}$ values for TFV also appeared to increase with increasing dose across the dose range on Days 1 and 13. Systemic exposure ($AUC_{0\text{-}24hr}$) to TFV did not appear to consistently change following repeated administration. Following the highest dose administered vaginally (25/20 mg TAF/EVG), mean TFV $AUC_{0\text{-}24hr}$ was 861 hr*ng/ml on Day 1 and 1400 hr*ng/ml on Day 13.[19]

TAF/EVG Insert – Rectal Irritation Study of EVG/TAF in Rabbits

CONRAD Study 1645-117 evaluated potential local irritation and determined the PK following once daily intrarectal administration of EVG and TAF to male and female rabbits for 14 consecutive days. PK assessments and analysis are summarized below.

Median peak EVG plasma concentrations were observed by 0.5 hours postdose on Days 1 and 13. Mean C_{max} values, ranging from 2.42 to 8.31 ng/mL, for EVG appeared to increase with increasing dose across the dose range on Days 1 and 13. Mean $AUC_{0\text{-}24hr}$ values did not appear to increase with increasing dose on Day 1 and appeared to increase with increasing dose across the dose range on Day 13. Systemic exposure ($AUC_{0\text{-}24hr}$) to EVG did not appear to consistently change following repeated administration of 4 mg EVG in combination with 5 mg TAF, however, appeared to increase following repeated administration of 12 and 20 mg EVG in combination with 15 and 25 mg TAF, respectively. Following the highest dose administered rectally (25/20 mg TAF/EVG), mean EVG $AUC_{0\text{-}24hr}$ was 22.1 hr*ng/ml on Day 1 and 58.2 hr*ng/ml on Day 13.[20]

Median peak TFV plasma concentrations were observed by 0.5 hours postdose on Days 1 and 13. Mean C_{max} values, ranging from 13.6 to 128, for TFV appeared to increase with increasing dose across the dose range on Days 1 and 13. Mean AUC_{0-24hr} values for TFV also appeared to increase with increasing dose across the dose range on Days 1 and 13. Systemic exposure (AUC_{0-24hr}) to TFV generally appeared to increase following repeated administration of EVG in combination with TAF. Following the highest dose administered rectally (25/20 mg TAF/EVG), mean TFV AUC_{0-24hr} was 11.6 hr*ng/ml on Day 1 and 33.9 hr*ng/ml on Day 13.

2.6.2.2 Toxicity

TAF/EVG Insert – Vaginal Irritation Study of EVG/TAF in Rabbits

CONRAD Study 1645-116 evaluated potential local irritation and determined the PK following once daily intravaginal administration of EVG and TAF to female rabbits for 14 consecutive days. 24 female rabbits were randomized to 6 groups: vehicle control, placebo control, reference control (N-9), or 4/5, 12/15, or 20/25 mg EVG/TAF. The assessment of toxicity in this study was made based on mortality, clinical observations, body weights, vaginal irritation scoring, micro and macroscopic pathology of reproductive tissues. Results can be found in the TAF/EVG insert IB.[14]

TAF/EVG Insert – Rectal Irritation Study of EVG/TAF in Rabbits

CONRAD Study 1645-117 evaluated potential local irritation and determined the PK following once daily intrarectal administration of EVG and TAF to male and female rabbits for 14 consecutive days. 24 male and 24 female rabbits were randomized to 6 groups for drug administration at a dose level of 4/5, 12/15, or 20/25 mg (EVG/TAF). The assessment of toxicity in this study was made based on mortality, clinical observations, body weights and body weight change. All animals survived to study termination on Day 14. There were no test article-related or definitive control article-related effects observed on study for the following parameters evaluated: bodyweights, clinical observations, macroscopic or microscopic pathology of tissues. TAF/EVG insert was generally safe and well tolerated by the rabbits in the study.[21]

All macroscopic findings were considered incidental changes as they lacked microscopic correlates, had no dose relationship in incidence or severity, occurred at a low incidence or as a single occurrence, or are known background incidental findings for the species. Both edema and mucosal hyperplasia were noted in males and females in the vehicle control, placebo control, and all test article-treated groups. These findings are considered most likely to be related to the procedure of intrarectal administration. There was a slight increase in severity in edema within the 12/15 and 20/25 mg EVG/TAF groups, but this was not considered test article related given the low incidence and variation in appearance of edema within the tissues.[21]

2.7 Clinical Studies of Elvitegravir and Tenofovir Alafenamide

2.7.1 Resistance (HIV)

2.7.1.1 EVG

Pooled resistance analysis was performed on virus samples from subjects receiving EVG-containing regimens in 6 clinical trials of EVG (as single drug in combination with a regimen containing a protease inhibitor/ritonavir or as the fixed dose combination STRIBILD). Development of substitutions T66A/I/K, E92G/Q, T97A, S147G, Q148H/K/R, and N155H in the HIV-1 integrase protein was primarily associated with resistance to EVG. In addition to these primary EVG resistance-associated substitutions, E92A, F121C/Y, P145S, Q146I/L/R, and N155S were also occasionally observed and were shown to confer reduced susceptibility to EVG. Substitutions at positions E92 and N155 were the most frequently observed (39% and 27% of those evaluated subjects, respectively). In virus isolates harboring the observed primary EVG resistance-associated substitutions, additional substitutions in integrase were detected including H51Y, L68I/V, G70R, V72A/N, I73V, Q95K/R, S119R, E138A/K, G140A/C/S, E157Q, K160N, E170A,S230R, and D232N.[7]

2.7.1.2 TAF

In Treatment-Naïve Subjects:

In a pooled analysis of antiretroviral-naïve subjects receiving GENVOYA in Studies 104 and 111, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 144, or at time of early study drug discontinuation. As of Week 144, the development of genotypic resistance to elvitegravir, emtricitabine, or TAF was observed in 12 of 22 subjects with evaluable resistance data from paired baseline and GENVOYA treatment-failure isolates (12 of 866 subjects [1.4%]) compared with 13 of 20 treatment-failure isolates from subjects with evaluable resistance data in the STRIBILD treatment group (13 of 867 subjects [1.5%]). Of the 12 subjects with resistance development in the GENVOYA group, the resistance-associated substitutions that emerged were M184V/I (N=11) and K65R/N (N=2) in reverse transcriptase and T66T/A/I/V (N=2), E92Q (N=4), E138K (N=1), Q148Q/R (N=1) and N155H (N=2) in integrase. Of the 13 subjects with resistance development in the STRIBILD group, the resistance-associated substitutions that emerged were M184V/I (N=9), K65R/N (N=4), and L210W (N=1) in reverse transcriptase and E92Q/V (N=4), E138K (N=3), Q148R (N=2), and N155H/S (N=3) in integrase. In both treatment groups, most subjects who developed substitutions associated with resistance to elvitegravir also developed emtricitabine resistance-associated substitutions. These genotypic resistance results were confirmed by phenotypic analyses.[13]

In Virologically Suppressed Subjects:

Three virologic failure subjects were identified with emergent genotypic and phenotypic resistance to GENVOYA (all three with M184I or V and one with K219Q in reverse transcriptase; two with E92Q or G in integrase) out of 8 virologic failure subjects with resistance data in a clinical study of virologically-suppressed subjects who switched from a regimen containing emtricitabine/TDF and a third agent to GENVOYA (Study 109, N=959).[13]

2.7.2 Pharmacokinetics of EVG and TAF

Oral EVG

Oral EVG must be co-administered with a pharmacokinetic booster to ensure adequate serum concentrations and facilitate once-daily dosing. Following oral administration of EVG and ritonavir with food, in HIV-1 infected subjects, peak EVG plasma concentrations were observed approximately 4 hours post-dose. EVG plasma exposures increased in a less than dose proportional manner, likely due to solubility-limited absorption.[22]

As EVG is metabolized by CYP3A, drugs that induce CYP3A activity are expected to increase the clearance of EVG. EVG undergoes primarily oxidative metabolism via CYP3A, and is secondarily glucuronidated via UGT1A1/3 enzymes. The median terminal plasma half-life of EVG following administration of EVG and ritonavir was approximately 8.7 hours.[22]

Oral TAF

A single-center, open-label, dose-ranging PK study investigated a single TAF dose in 24 healthy, premenopausal HIV seronegative female volunteers 18-49 years old. They were given 5, 10 or 25mg of TAF and each participant provided plasma, PBMC and cervical, vaginal and rectal tissue samples over 14 days. For each group, median (IQR) tenofovir plasma $AUC_{0–14}$ days was 52.8 (49.5–59.6), 78.1 (68.2–86.9) and 169.7 (131.2-211.4) ng-h/mL and tenofovir-dp PBMC $AUC_{0–14}$ days was 2268 (1519-4090), 4584 (3113-5734) and 9306 (6891-10785) fmol-h/106 cells, respectively. Tenofovir was quantifiable in 52% and 92% of FGT and GI tissues, whereas tenofovir-dp was quantifiable in only 5% and 19% of female genital tract and lower gastrointestinal tissues, respectively. Plasma tenofovir and PBMC tenofovir-dp were dose proportional (90% CI 0.87-1.15 and 0.62-1.02, respectively).[23]

In a study of safety, antiviral activity, and pharmacokinetics of TAF, non-cirrhotic, treatment-naïve subjects with chronic hepatitis B were randomized (1:1:1:1:1) to receive TAF 8, 25, 40, or 120 mg, or TDF 300 mg for 28 days and assessed for safety, antiviral response, and pharmacokinetics, followed-up by off-treatment for 4 weeks. Following single dose administration on day 1, concentrations of TAF in plasma increased in proportion to dose, reaching maximum concentrations within 30-40 minutes. Consistent with the short elimination half-life of TAF (<45 min), plasma concentrations of the drug were below the limit of quantification 6-8 hours following dosing. TAF was completely undetectable in trough (pre-dose) plasma samples, collected over the 28 day dosing period. At each of the dose levels evaluated, mean plasma TFV concentrations following administration of TAF were substantially lower than those following TDF dosing. Relative to the mean TFV exposure (AUC_{inf}) with TDF 300 mg (2267 ng-h/ml), percentage reductions in mean TFV exposures for TAF of 97%, 92%, 81%, and 33%, were seen following TAF doses of 8, 25, 40, and 120 mg, respectively.[24]

In another study of pharmacokinetics, safety and antiviral activity of 40 or 120 mg of TAF compared with 300 mg of TDF, TAF and TDF were administered as monotherapy once daily for 14 days in 30 HIV-1-infected, treatment-naive subjects. Administration of 40 mg

TAF resulted in lower tenofovir Cmax (13 versus 207 ng/mL) and lower systemic exposures (AUC_{0-t}, 383 versus 1810 ng-h/mL) compared with subjects who received TDF. There were higher intracellular tenofovir concentrations within peripheral blood mononuclear cells with both 40 mg (8.2 uM) and 120 mg (16.9 uM) of TAF compared with 300 mg of TDF (0.9 uM).[25]

A phase 1b, randomized, partially blinded, active- and placebo-controlled, dose-ranging study was also conducted with 38 treatment-naive and experienced HIV-1–positive adults currently off antiretroviral therapy. Participants were randomized to receive 8, 25, or 40 mg TAF, 300 mg TDF, or placebo, each once daily for 10 days. After administration of 8, 25, or 40 mg TAF, TAF was rapidly absorbed (median Tmax ~0.50 hours), displayed a short plasma half-life (t½ ;0.40 hours), and was below the limit of quantitation in plasma by ~5 hours post-dose. After administration of 8, 25, or 40 mg TAF or 300 mg TDF, the highest TFV plasma concentrations were observed with TDF. At steady state, 8, 25, and 40 mg TAF yielded mean TFV plasma exposures AUC_{tau} of 97%, 86%, and 79% lower, respectively, as compared with the TFV exposures observed with 300 mg TDF. For 25 and 40 mg TAF, the mean intracellular peripheral blood mononuclear cell tenofovir-dp AUC_{tau} was ~7-fold and ~25-fold higher relative to 300 mg TDF.[26]

Oral EVG and TAF in combination therapy

A single-arm, open-label study was conducted in 50 treatment-naïve adolescents with HIV aged 12-18 years from ten hospital clinics in South Africa, Thailand, Uganda, and the USA. The study aimed to assess safety, pharmacokinetics, and efficacy of the single-tablet, fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (Genvoya®). The mean AUC_{tau} for EVG was 23840 ng-h per mL (CV 25.5%), and the mean AUC_{last} for TAF was 189 ng-h per mL (CV 55.8%). Both the AUC_{las} and Cmax of TAF in adolescents were similar to those noted in adults after administration of Genvoya. Notably, tenofovir exposure in adolescents following this administration was more than 90% lower than tenofovir exposure following this administration in adults.[27]

In a single-arm, multicenter, open-label Phase 3 study, Genvoya was administered once daily to 242 virologically suppressed HIV-1-infected participants with renal impairment to assess it safety and efficacy. Plasma PK parameters was measured in a subset of patients who participated in the intensive PK substudy (n = 30). The EVG and cobicistat (COBI) PK parameters were in the range of historical data after administration of Genvoya in HIV infected patients without renal impairment. TAF PK parameters were consistent with historical data in nonrenally impaired patients. Additionally, the TAF metabolite TFV was higher in patients in this study vs historical TAF data in nonrenally impaired patients but was well below the TFV exposures from TDF-containing regimens.[28]

Two controlled, double-blind, Phase 3 studies were conducted to compare the safety and efficacy of E/C/F/TAF versus E/C/F/TDF in 1733 treatment-naive HIV-infected patients from 178 outpatient centers in 16 countries. Participants were randomly assigned (1:1) to receive once-daily oral tablets containing 150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide (E/C/F/TAF) or 300 mg tenofovir disoproxil fumarate (E/C/F/TDF) with matching placebo. 65 participants participated in the intensive pharmacokinetic Substudy. Of those, 35 patients participated in the PBMC

substudy. Plasma tenofovir exposure AUC_{tau} after administration of E/C/F/TAF was 91% lower than tenofovir exposure achieved with E/C/F/TDF. The PBMC tenofovir-dp AUC_{tau} was 4.1 times higher in participants receiving E/C/F/TAF than in those receiving E/C/F/TDF.[29]

Insert: Placebo and Drug-containing (TFV/FTC)

CONRAD 117 was a randomized, double blind, placebo-controlled, Phase 1 trial designed to evaluate safety, PK/PD, and disintegration time after a single use of a vaginal insert containing TFV and/or FTC and during and after 14 days of once-daily use. 49 women were randomized 1:1:1:1 to use inserts containing 40 mg TFV, 40 mg FTC, 40 mg TFV + 40 mg FTC, or placebo. Participants self-administered one insert per day for 14 days. The TFV levels in vaginal aspirate were similar to those after TFV 1% vaginal gel administration associated with protection in a previous clinical study, and levels of TFV-DP in vaginal tissue associated with protection in a nonhuman primate study. Levels of FTC in aspirate and FTC-TP in genital tissue appeared to be at least as high as those seen after oral dosing in women and macaques. Systemic levels of both TFV and FTC were low.[14]

TAF/EVG Vaginal Insert

CONRAD will conduct A18-146, a Phase 1 clinical trial of the TAF/EVG vaginal insert. This will be the first-in-human study for the vaginally administered TAF/EVG insert and will evaluate the safety, tolerability, PK, and PD after a single dose. The study will recruit healthy, non-pregnant women aged 18-50 years who are not at risk for pregnancy and at low risk for sexually transmitted infections. Participants will use a single TAF/EVG insert in the clinic and will be randomized to 1 of 2 sample collection groups (2 and 48 hours after dosing or 24 and 72 hours after dosing). Plasma, cervicovaginal fluid and cervical tissue for PK will collected. It is expected that much lower plasma concentrations will be obtained for all drugs and aid in demonstrating systemic safety and refuting the need for further or extensive systemic PK characterization.[14] CONRAD will keep MTN apprised of any serious AEs that occur in this study.

2.7.3 Safety of EVG and TAF

Oral EVG is currently approved for use as part of combination therapy. For the treatment of HIV infection, oral TAF is also approved for use as part of combination therapies. Therefore, large scale studies examining the safety and tolerability of EVG and TAF are limited to clinical trials where EVG or TAF were administered in combination with other ARVs.

Oral EVG

Gilead Study GS-US-183-0101 demonstrated minimal AEs with the use of oral EVG. The study was a randomized, double-blind, placebo controlled, monotherapy phase 1/2 trial with 40 HIV-1 infected participants – a mix of both treatment naïve and treatment experienced (but not currently receiving ARV therapy) individuals. Participants received EVG or placebo for 10 days at 5 dosage levels: 200 mg BID, 400 mg BID, 800 mg QD, 800 mg BID, or 50 mg + 100 mg ritonavir QD. TEAEs of grade 2 or 3 were reported in

27% of participants receiving EVG and 40% of those receiving placebo; no participants reported serious AEs, dosage interruptions, or discontinued from the study.[8]

Oral TAF

The safety of TAF(Vemlidy®) was assessed based on pooled data through the Week 96 data analysis from 1298 subjects in two randomized, double-blind, active-controlled trials (Gilead Study 108 and Study 110), in adult subjects with chronic hepatitis B and compensated liver disease. The most common adverse reaction (all Grades) reported in at least 10% of subjects in the TAF group was headache. The proportion of subjects who discontinued treatment with TAF or TDF due to adverse reactions of any severity was 1.5% and 0.9%, respectively. Table 5 displays the frequency of the adverse reactions (all Grades) greater than or equal to 5% in the TAF group.[12]

Table 5: Adverse Reactions[a] (All Grades) Reported in ≥5% of Subjects with Chronic HBV Infection and Compensated Liver Disease in Studies Gilead Studies 108 and 110 (Week 96 Analysis[b])

Adverse reaction	Tenofovir alafenamide (TAF) N=866	Tenofovir Disoproxil Fumarate (TDF) N=432
Headache	12%	10%
Abdominal pain[c]	9%	6%
Cough	8%	8%
Back pain	6%	6%
Fatigue	6%	5%
Nausea	6%	6%
Arthralgia	5%	6%
Diarrhea	5%	5%
Dyspepsia	5%	5%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study product.
b. Double-bind phase
c. Grouped term including abdominal pain upper, abdominal pain, abdominal pain lower, and abdominal tenderness.

EVG and TAF in Combination Therapy

Additional clinical trials of EVG or TAF in HIV-infected individuals were conducted with EVG and TAF as part of combination therapy, administered in combination with other antiretrovirals; thus it is not possible to attribute individual AEs to EVG or TAF.[8] Genvoya is a four drug combination that includes EVG, cobicistat, emtricitabine and TAF.

In clinical trials in antiretroviral treatment-naïve HIV-infected adults, the primary safety assessment of Genvoya was based on Week 144 pooled data from 1733 subjects from two randomized, double-blind, active-controlled trials – Gilead Studies 104 and 111. A total of 866 subjects received one tablet of Genvoya once daily.

The most common adverse event (all grades) reported in at least 10% of subjects in the Genvoya group was nausea. The proportion of subjects who discontinued treatment with Genvoya or Stribild due to AEs (regardless of severity) was 1% and 2%, respectively. The majority of AEs were grade 1. See Table 6 for the frequency of AEs (all grades) ≥5% in the Genvoya group.

Table 6: Adverse Reactions (All Grades) Reported in ≥5% of HIV-1 Infected Treatment-Naïve Adults Receiving Genvoya or Stribild in Gilead Studies 104 and 111 (Week 144 Analysis)

Adverse reaction	Genvoya N=866	Stribild N=867
Nausea	11%	13%
Diarrhea	7%	9%
Headache	6%	5%
Fatigue	5%	4%

Insert: Placebo and Drug-containing (TFV/FTC)

In CONRAD 134, an open-label study that assessed in-vivo disintegration time, safety, and product acceptability of 4 placebo vaginal inserts in 32 women aged 18-50 who were not at risk of pregnancy – placebo inserts were found to be safe, with one mild AE reported that was subsequently assessed as being unrelated to study drug. The optimized insert prototypes were found to disintegrate faster and have higher acceptability over first generation inserts.[8,30]

In CONRAD 117, the first-in-human study of vaginal microbicide inserts using TFV and/or FTC containing vaginal inserts - treatment-emergent adverse events (TEAEs) were minimal; only one TEAE met the pre-specified criterion for the safety endpoint, but this event was in the placebo group. Colposcopy and physical exam findings were minimal, as were changes in microflora and systemic laboratory values.[8]

2.7.4 Efficacy

Efficacy data for EVG or TAF containing antiretroviral regimens is summarized in the IB, and in the package inserts for EVG/COBI/FTC/TDF (Stribild, Gilead Sciences, Inc.) and EVG/COBI/FTC/TAF (Genvoya, Gilead Sciences, Inc.).[13]

2.8 Study Hypotheses and Rationale for Study Design

2.8.1 Study Primary Hypotheses

It is hypothesized that the two dose levels of the TAF/EVG Insert in this study will be safe when applied to the rectum and well-tolerated among healthy individuals who have a history of receptive anal intercourse (RAI).

2.8.2 Rationale for Study Design

Rectal microbicides are needed for individuals at risk of acquiring HIV infection through unprotected RAI. It is important to expand the rectal microbicide pipeline with the addition of products from different classes such as EVG, an integrase inhibitor, and TAF, a nucleotide reverse transcriptase inhibitor.

Rationale for the Dosing and PK Sampling Schedule

MTN-039 is the first study to assess the safety and PK of the TAF/EVG Insert applied rectally. Antiviral activity studies of EVG in tissue explant models have shown that an EVG tissue concentration of at least 1000 ng/g will be efficacious prophylactically against HIV infection. Previous vaginal PK/PD studies suggested that a concentration of 1000 fmol/mg TFV-DP in tissue could be a good predictor of high efficacy against HIV infection.[31] Based on the preclinical and animal data collected to date, the TAF/EVG insert with 20 mg TAF and 16 mg EVG doses will achieve the target tissue concentration of 1000 ng/g EVG and 1000 fmol/mg TFV-DP in humans.

The PK sampling schedule in this study will provide valuable information regarding the rectal TAF/EVG PK profile in humans. This will provide guidance for ongoing product development efforts to develop a combination topical insert containing TAF and EVG.

3 OBJECTIVES

3.1 Primary Objectives

Safety

- To evaluate the safety of the TAF/EVG Insert, 20/16 mg administered rectally at two dose levels: 1 insert and 2 inserts

Pharmacokinetics

- To characterize the systemic and rectal pharmacokinetics of the TAF/EVG Insert, 20/16 mg applied rectally at two dose levels: 1 insert and 2 inserts

3.2 Secondary Objective

Acceptability

- To identify product attributes considered likely to challenge and/or facilitate future sustained use of a TAF/EVG insert applied rectally

3.3 Exploratory Objectives

***Ex Vivo* Efficacy**

- To assess the preliminary (*ex vivo)* efficacy of TAF/EVG after product is inserted rectally

Pharmacokinetics

- To characterize the cervicovaginal pharmacokinetics of the TAF/EVG Insert, 20/16 mg applied rectally at two dose levels: 1 insert and 2 inserts

Mucosal Safety

- To evaluate mucosal safety of the TAF/EVG Insert, 20/16 mg applied rectally at two dose levels: 1 insert and 2 inserts

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-039 is a phase 1, multi-site, open-label, single arm, two-period study of rectal administration of one TAF/EVG Insert, 20/16 mg and then two TAF/EVG Inserts.

4.2 Summary of Major Endpoints

Primary Endpoints:

Safety

- All Grade 2 and higher AEs

Pharmacokinetics

- EVG concentrations in:
  - Blood
  - Rectal fluid
  - Rectal mucosal tissue homogenates

- TAF and TFV concentrations in:
  - Blood
  - Rectal fluid

- TFV-DP concentration in:
  - Rectal mucosal tissue homogenates
  - Rectal mucosal tissue cell isolates

Secondary Endpoint:

Acceptability

- Participant report of overall acceptability of the TAF/EVG Insert applied rectally

Exploratory Endpoints:

***Ex Vivo* Efficacy**

- Changes in HIV-1 replication in colorectal explant culture supernatant
- Anti-HIV activity in rectal fluid
- Anti-HIV activity in cervicovaginal fluid

Pharmacokinetics

- EVG, TAF and TFV concentrations in cervicovaginal fluid

Mucosal Safety

- Rectal histology
- Rectal proteomics
- Rectal metabolomics
- Rectal immunophenotype
- Rectal microbiome
- Cervicovaginal microflora

4.3 Description of Study Population

The study population will consist of HIV-uninfected individuals 18 years of age or older who meet the criteria outlined in Sections 5.2 and 5.3.

4.4 Time to Complete Accrual

The time to complete accrual is anticipated to be approximately 6-8 months.

4.5 Study Groups

MTN-039 will enroll approximately 20 evaluable participants.

4.6 Expected Duration of Participation

Each participant will be on study for approximately 6-13 weeks. The total duration of the study will be approximately 11 months.

4.7 Sites

Sites selected by the MTN Executive Committee.

5 STUDY POPULATION

5.1 Selection of the Study Population

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

5.1.1 Recruitment

Participants will be recruited from a variety of sources, including outpatient clinics, universities and community-based locations. Recruitment materials will be approved by

site Institutional Review Boards (IRBs) prior to use.

5.1.2 Retention

Once a participant is enrolled in MTN-039, study sites will make every effort to retain the participant in follow-up to minimize possible bias associated with loss-to-follow-up. Sites will be responsible for developing and implementing local standard operating procedures (SOPs) to target and ensure high rates of retention.

5.2 Inclusion Criteria

Individuals who meet the following criteria are eligible for study inclusion:

1) Individuals who are 18 years of age or older at Screening, verified per site SOP

2) Able and willing to provide written informed consent to be screened for and enrolled in MTN-039

3) HIV-1/2 uninfected at Screening and Enrollment, per applicable algorithm in Appendix II and willing to receive HIV test results

4) Able and willing to provide adequate locator information, as defined in site SOP

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) In general good health at Screening and Enrollment, as determined by the site IoR or designee

8) At Screening, history of consensual RAI at least once in lifetime per participant report

9) Willing not to take part in other research studies involving drugs, medical devices, genital or rectal products, or vaccines for the duration of study participation (including the time between Screening and Enrollment)

10) Willing to comply with abstinence and other protocol requirements as outlined in Section 6.7

11) For participants of childbearing potential: a negative pregnancy test at Screening and Enrollment

12) For participants of childbearing potential: Per participant report at Enrollment, using an effective method of contraception for at least 30 days (inclusive) prior to Enrollment and intending to use an effective method for the duration of study participation. Effective methods include:
    - Hormonal methods
    - Intrauterine device (IUD) inserted at least 30 days prior to Enrollment (but not past the maximum length of recommended usage according to package instructions)
    - Sterilization (of participant or partner, as defined in site SOPs)

- 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; this includes having sex exclusively with individuals assigned female sex at birth

5.3 Exclusion Criteria

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

1) At Screening:
    a) Hemoglobin Grade 1 or higher*
    b) Platelet count Grade 1 or higher*
    c) Aspartate aminotransferase (AST) or alanine transaminase (ALT) Grade 1 or higher*
    d) Serum creatinine >1.3× the site laboratory upper limit of normal (ULN)
    e) International normalized ratio (INR) >1.5× the site laboratory ULN
    f) History of inflammatory bowel disease by participant report

    **As per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017.*

    Note: Otherwise eligible participants with an exclusionary test result (other than HIV) can 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.

2) Anticipated use of and/or unwillingness to abstain from the following medications during study participation:
    a) Anticoagulant medications
    b) Non-study rectally-administered medications and any products containing N-9

3) Known adverse reaction to any of the components of the study product

4) Use of pre-exposure prophylaxis (PrEP) for HIV prevention within 3 months prior to Enrollment, and/or anticipated use and/or unwillingness to abstain from PrEP during trial participation

5) Use of post-exposure prophylaxis (PEP) for potential HIV exposure within 6 months prior to Enrollment

6) Condomless RAI and/or penile-vaginal intercourse with a partner who is known to be HIV-positive or whose status is unknown in the 6 months prior to Enrollment

7) History of transactional sex in the 12 months prior to Enrollment

8) Non-therapeutic injection drug use or use of non-therapeutic, non-injection stimulant drugs in the 12 months prior to Enrollment

9) Participation in research studies involving drugs, medical devices, genital or rectal products, or vaccines within 30 days of the Enrollment Visit

10) Per participant report, medical records, clinical diagnosis and/or diagnostic testing at either Screening or Enrollment:

a. Diagnosis or treatment of an anogenital STI in the 3 months prior to enrollment (including window between Screening and Enrollment).

b. Symptoms, clinical or laboratory diagnosis of active pharyngeal, anorectal, or reproductive tract infection (RTI) requiring treatment per current CDC guidelines (http://www.cdc.gov/std/treatment).

c. Current symptomatic urinary tract infection (UTI).

Infections requiring treatment include Neisseria gonorrhea (GC), Chlamydia trachomatis (CT) infection, syphilis, active herpes simplex virus (HSV) lesions, or symptomatic genital warts, chancroid, pelvic inflammatory disease (PID), bacterial vaginosis (BV), symptomatic vaginal candidiasis, and trichomoniasis.

Note: Otherwise eligible participants with an exclusionary UTI, BV and/or candida finding may be re-tested during the screening process.

11) For participants of childbearing potential: Pregnant or breastfeeding at either Screening or Enrollment or planning to become pregnant during study participation

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

12) For participants of childbearing potential: Last pregnancy outcome 90 days or less prior to Screening

13) 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.

5.4 Co-enrollment Guidelines

As indicated in Sections 5.2 and 5.3, participants must not take part in other research studies involving drugs, medical devices, rectal and genital products, or vaccines after the Screening Visit and while taking part in MTN-039 unless approved by the Protocol Safety Review Team (PSRT). Participation in the following types of studies may be allowed at the discretion of the IoR/designee:

- Participants may take part in ancillary studies if approved by MTN-039 PSRT

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-039, the IoR/designee will consult the PSRT regarding ongoing product use and other potential safety considerations associated with co-enrollment.

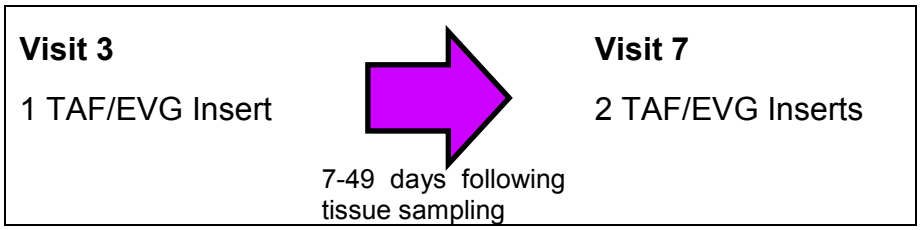
6 STUDY PRODUCT

6.1 Regimen

The product being used in this study is Tenofovir Alafenamide (TAF)/Elvitegravir (EVG) Vaginal Insert 20/16 mg. This product was initially developed for a study (A18-146) involving vaginal administration, however rectal administration of the product is now being studied in this trial. Therefore, the product can simply be referred to as "TAF/EVG Insert" for this study. Each insert for rectal administration contains 20 mg tenofovir alafenamide (TAF) and 16 mg elvitegravir (EVG).

Participants will self-administer a saline enema at home the evening prior to a clinic dosing visit. Each participant will receive a single TAF/EVG Insert for rectal administration. After a washout period of at least 7 days, participants will each receive two TAF/EVG Inserts for rectal administration. After each dose is administered in the clinic, PK and PD sampling will be conducted over a three-day period.

Table 7: Study Product Regimen



6.2 Administration

Participants will be instructed to present to the clinic for each of the 2 doses of rectally administered TAF/EVG Inserts. Administration of the TAF/EVG Insert(s) will be performed by study staff.

6.3 Study Product Formulation and Storage

Normal Saline Home Enemas

Participants will be provided with two 120 mL sealed cups of sterile USP normal saline (NS) solution for home enema administration. The participant will use a 60 mL oral syringe (provided) to transfer the entire content of the NS cup to the enema bottle. Although all of the solution should be transferred to the enema bottle, the participant will be instructed to discard any unused solution remaining in the original container. The NS solution should be stored at room temperature 25ºC (77°F). Additionally, participants will be instructed to dispose the prepared saline enema if not used within 24 hours of filling.

Each participant will receive a sheet of instructions which will outline the process for preparing the enema, disposing unused solution and enema administration. A review of these instructions will be conducted with the participant at the clinic prior to providing the enema kit to be administered at home.

TAF/EVG Inserts

TAF/EVG Inserts have been formulated into white to off-white uncoated bullet shaped inserts containing 22.40 mg of TAF Fumarate (equivalent to 20 mg TAF free base) and 16 mg of EVG. TAF is a nucleotide reverse transcriptase inhibitor (NRTI) and a prodrug of Tenofovir (TFV) and EVG is an integrase inhibitor. Both the active pharmaceutical ingredients (APIs) are supplied by Gilead Sciences, Inc.

Figure 2: Study Product

In addition to TAF and EVG this insert contains the following inactive excipients: povidone, magnesium stearate, polaxomer (also known as Kolliphor P188), polyethylene glycol, mannitol, and lactose anhydrous. The insert dimensions are: length: 1.5 cm (0.6 inches), width: 0.7 cm (0.28 inches), height: 0.6 cm (0.23 inches). Each insert is approximately 500 mg in weight. The TAF/EVG Insert should be stored as supplied in a white induction-sealed HDPE bottle of 20 inserts along with polyester coil and a desiccant at room temperature (20° - 25°C) (68° - 77°F) until dispensed for use. Excursions between 15 ° - 30°C (59° - 86°F) are allowed.

6.4 Study Product Supply and Accountability

6.4.1 Study Product Supply

CONRAD (the organization that supplies the rectal insert) will oversee the manufacture and analysis/release (Patheon, Whitby, ON, Canada) of the study product under current Good Manufacturing Practices (cGMP).

Sealed cups containing 120 mL USP normal saline and USP are supplied by Nurse Assist, Inc, Fort Worth. The enema bottles used in this study are commercially available 125 mL enema bottles that meet US Pharmacopeia (USP) standards and contain no heavy metals, no phthalates, and are bisphenol A (BPA) free.

6.4.2 Study Product Dispensing

TAF/EVG Inserts will be dispensed to clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. An authorized prescriber includes the IoR or a licensed clinician directly responsible to the IoR as noted on the Form FDA 1572.

6.4.3 Study Product Accountability

Each Clinical Research Site (CRS) Pharmacist of Record (PoR) is required to maintain a complete record of all TAF/EVG Inserts received and subsequently dispensed. All unused TAF/EVG Inserts 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-039 Pharmacy Study Product Management Procedures Manual.

6.5 Ancillary Study Supplies

Clinic staff will provide male condoms to all participants. Lubricant will be provided at each dosing for ease of administration (if needed).

6.6 Concomitant Medications

Enrolled study participants may use concomitant medications during study participation except for medications and products not permitted per the inclusion and exclusion criteria and listed in Section 6.7 below. All concomitant medications reported throughout the course of the study will be recorded in the study database. Concomitant medications include all prescription medications, over-the-counter preparations, vitamins, nutritional supplements, and herbal preparations.

6.7 Prohibited Medications, Products and Practices

6.7.1 Prohibited Medications and Products

Several concomitant medications/practices will not be permitted. Participants are prohibited from using strong and moderate CYP3A inhibitors and inducers. These medications are not permitted because EVG is a CYP3A substrate. A listing of these specific prohibited agents is provided below (see Table 8 and Table 9) and in the MTN-039 SSP Manual available at www.mtnstopshiv.org. Mild inducers/inhibitors are permitted as long as stable dose is anticipated throughout the study.

Table 8: Prohibited CYP Inhibitors

Strong Inhibitors **≥ 5-fold increase in AUC** **or > 80% decrease in CL**	**Moderate Inhibitors** **≥2 but < 5-fold increase in** **AUC or 50-80% decrease in CL**
Antibiotics: clarithromycin, telithromycin Antidepressants: nefazodone Azole Antifungals: ketoconazole, itraconazole, posaconazole, voriconazole Pharmacokinetic Enhancers: cobicistat Protease Inhibitors: ritonavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, boceprevir, telaprevir Reverse Transcriptase Inhibitors: delavirdine Vasopression Receptor Antagonists: conivaptan	Antiarrhythmics: dronedarone Antibiotics: erythromycin, ciprofloxacin Antiemetics: aprepitant Antineoplastics: imatinib Azole Antifungals: fluconazole, miconazole Calcium Channel Blockers: verapamil, diltiazem Protease Inhibitors: atazanavir, darunavir/ritonavir, fosamprenavir

Table 9: Prohibited CYP Inducers

Strong Inducers **≥ 80% decrease in AUC**	**Moderate Inducers** **50-80% decrease in AUC**
Anticonvulsants/Mood Stabilizers: phenytoin, carbamazepine Anticonvulsants/Barbiturates: primidone Antituberculars: rifampin Barbiturates: phenobarbital, butalbital Glucocorticoids: dexamethasone Herbal Supplements: St. John's wort^ Protease Inhibitors: tipranavir (alone)	Antibiotics: nafcillin Antihypertensives: bosentan Antituberculars: rifabutin CNS Stimulants: modafinil Reverse Transcriptase Inhibitors: efavirenz, etravirine, nevirapine

^The effect of St. John's wort and echinacea varies widely and is preparation-dependent.

The use of study product concurrently with PEP and PrEP is prohibited during study participation. Individuals who need PEP or PrEP due to known or potential HIV exposure will permanently discontinue study product use. See Section 9.3 for additional information. Use of rectally-administered medications and products, including N-9 products, is also prohibited.

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

Participants will be counseled to abstain from using aspirin (greater than 81 mg) and non-steroidal anti-inflammatory drugs (NSAIDS) within 72 hours prior to and following a tissue sample collection visit. Should a participant report taking any of the medications noted above, which may increase risk of bleeding, or report the use of rectal medications or products within 72 hours prior to tissue collection, 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.

6.7.2 Prohibited Practices

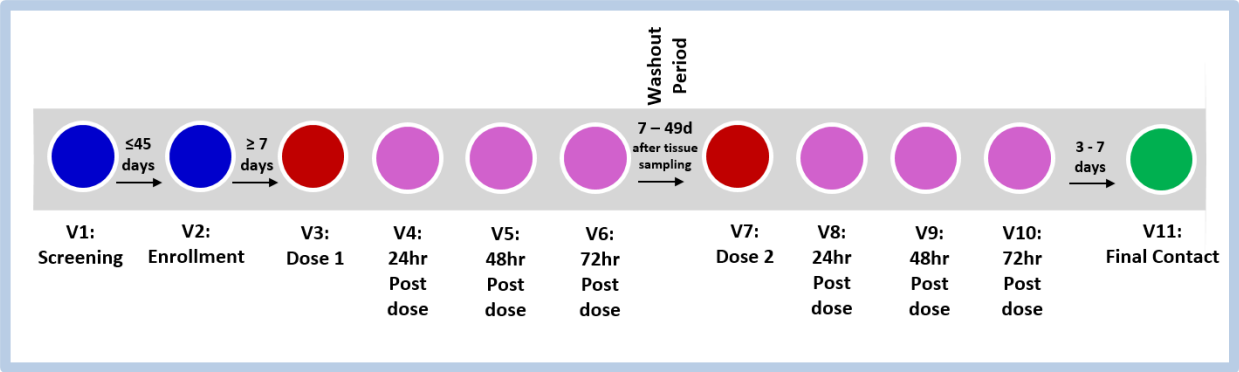
All participants are to abstain from inserting any non-study products (including rectal medications, enemas, lubricant and sex toys) into the rectum, rectal stimulation with fingers, receptive oral anogenital stimulation and receptive anal intercourse for 72 hours prior to and following clinic visits. Participants should abstain from inserting anything into the vagina for 72 hours prior to each clinic visit, including fingers, spermicides, vaginal medications (including hormones), vaginal douches, lubricants and moisturizers, sex toys (vibrators, dildos, etc.) and vaginal intercourse.

If desired, the IoR may request rapid PSRT consultation to assist in making the determination as to whether or not to proceed with the visit at that time or to reschedule an interim visit. If the decision is made to reschedule an interim visit, any missed procedures (including biopsy collection) should be performed during the interim visit.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is presented in Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures as well as information regarding the study visit windows are provided in the MTN-039 SSP Manual available at http://www.mtnstopshiv.org.

Figure 3: MTN-039 Study Visit Schedule



7.1 Pre-screening

As part of participant outreach and recruitment strategies, study staff can 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 study sites 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

A Screening Visit will 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 consent for Screening/Enrollment will be obtained before any screening procedures are initiated. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined.

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

Table 10: Screening Visit

Screening Visit - Visit 1	
Component	**Procedures**
Administrative and Regulatory	• Obtain written informed consent • Assign a unique Participant Identification (PTID) number • Assess eligibility • Collect demographic information • Collect locator information • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling	• HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Protocol counseling

Clinical		• Collect concomitant medications • Collect medical history • Perform physical examination • Perform genital examination* • Perform pelvic examination*▲ • Perform rectal examination • Treat or prescribe treatment for RTI/UTI, or STIs* • Provide available test results
Laboratory	**Pharyngeal**	• NAAT for GC/CT
	Urine	• NAAT for GC/CT▼ • Urine dipstick/culture* • Pregnancy test ■
	Blood	• CBC with differential and platelets • Chemistries (AST/ALT/creatinine) • Syphilis serology • HIV-1/2 test • Coagulation (PT/INR)
	Pelvic▲	• NAAT for GC/CT/TV
	Anorectal	• NAAT for GC/CT
Study Product/Supplies		• Offer condoms

* If indicated ▲Participants assigned female sex at birth and if anatomy allows ▼If pelvic GC/CT cannot be performed ■ Participants of childbearing potential

7.3 Enrollment (Day 0)

The Enrollment Visit can occur up to 45 days after the Screening Visit. All Enrollment procedures must occur on the same day.

Participants will be assigned to one of two groups to obtain samples: Group 1 will have biopsies, rectal fluid and cervicovaginal fluid (if applicable) collected at 2 hours (Visits 3 and 7) and 48 hours (Visits 5 and 9) following each administration of product; participants in this group will also have rectal and cervicovaginal fluid collected at 6 hour post-dose at Visits 3 and 7. Group 2 will have biopsies, rectal fluid and cervicovaginal fluid (if applicable) collected at 24 hours (Visits 4 and 8) and 72 hours (Visits 6 and 10) following each administration of product; participants in this group will also have rectal and cervicovaginal fluid collected at 4 hours post-dose at Visits 3 and 7. Both groups will have blood collected at each visit from Visit 3 through Visit 10. At least three participants assigned female sex at birth should be enrolled and assigned to each group.

Table 11: Enrollment Visit

Enrollment Visit – Visit 2	
Component	**Procedures**
Administrative and Regulatory	• Assess and confirm eligibility • Review/update locator information • Random assignment to sampling schedule • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling	• HIV pre- and post-test counseling

		• HIV/STI risk reduction counseling • Protocol counseling • Behavioral assessment (CASI)
Clinical		• Review/update concomitant medications • Review/update medical history • Perform physical examination • Perform genital examination* • Perform pelvic examination* ▲ • Perform rectal examination • Treat or prescribe treatment for RTI/UTI, or STIs* • Provide available test results
Laboratory	**Pharyngeal**	• NAAT for GC/CT*
	Urine	• NAAT for GC/CT* ▼ • Urine dipstick/culture* • Pregnancy test ■
	Blood	• CBC with differential and platelets* • Chemistries (AST/ALT/creatinine)* • Syphilis serology* • Plasma for archive • HIV-1/2 test • Blood for PK
	Pelvic ▲	• NAAT for GC/CT/TV* • CVF for PD • CVF for microflora
	Anorectal	• Rectal fluid for PD • Rectal fluid for microbiome • Rectal enema prior to biopsy collection • Rectal tissue for PD • Rectal tissue for biomarkers • NAAT for GC/CT*
Study Product/Supplies		• Offer condoms • Provide home enema kit

* If indicated ▲ Participants assigned female sex at birth and if anatomy allows ▼If pelvic GC/CT cannot be performed ■ Participants of childbearing potential

7.4 Follow-up Visits

7.4.1 Dosing – Visits 3 and 7

The first dosing visit (Visit 3) should occur at least 7 days after the Enrollment Visit. The second and final dosing visit (Visit 7) should occur at least 7 days after the last tissue sampling visit following Dose 1 (following Visit 5 or 6 with a 1- to 7-week washout period).

Table 12: Dosing Procedures

Dosing Procedures – Visits 3 and 7	
Component	**Procedures**

Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling		• HIV pre- and post-test counseling* • HIV/STI risk reduction counseling* • Protocol counseling
Clinical		• Review/update medical history • Review/update concomitant medications • Perform targeted physical examination* • Perform genital examination* • Perform pelvic examination* ▲ • Perform rectal examination • Treat or prescribe treatment for RTI/UTI, or STIs* • Provide available test results • Collect/update AEs
Laboratory	**Pharyngeal**	• NAAT for GC/CT*
	Urine	• NAAT for GC/CT*▼ • Urine dipstick/culture* • Pregnancy test*■
	Blood	• CBC with differential and platelets* • Chemistries (AST/ALT/creatinine)* • Syphilis serology* • HIV-1/2 test* • Blood for PK ♦
	Pelvic▲	• CVF for PK ** • CVF for PD ♣ • CVF for microflora ♣ • NAAT for GC/CT/TV*
	Anorectal	• Rectal fluid for PK ** • Rectal fluid for PD ♣ • Rectal fluid microbiome ♣ • Rectal tissue for PK ♣ • Rectal tissue for PD ♣ • Rectal tissue for biomarkers ♣ • NAAT for GC/CT*
Study Product/Supplies		• Administration of study product • Offer condoms • Offer lubricant

* If indicated ▲ Participants assigned female sex at birth and if anatomy allows ▼If pelvic GC/CT cannot be performed ■ Participants of childbearing potential

♦ All participants will have blood collected at 1, 2, 4, and 6 hours following product administration.

♣ Group 1 only at 2 hours post-dose

** Group 1: 2 and 6 hours post-dose; Group 2: 4 hours post-dose

7.4.2 Post-Dosing Visits – Visits 4 and 8

The 24-hour Post-Dosing Visits (Visits 4 and 8) should occur between 22 and 26 hours (+/- 2 hours) after each dosing visit.

Table 13: 24-hour Post-Dosing Visits

24-Hour Post-Dosing Visits - Visits 4 and 8		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling		• HIV pre- and post-test counseling* • HIV/STI risk reduction counseling* • Protocol counseling • Behavioral assessment (Brief CASI)
Clinical		• Review/update medical history • Review/update concomitant medications • Perform targeted physical examination* • Perform genital examination* • Perform pelvic examination* ▲ • Perform rectal examination • Treat or prescribe treatment for RTI/UTI, or STIs* • Provide available test results • Collect/update AEs
Laboratory	**Pharyngeal**	• NAAT for GC/CT*
	Urine	• NAAT for GC/CT* ▼ • Urine dipstick/culture* • Pregnancy test* ■
	Blood	• CBC with differential and platelets* • Chemistries (AST/ALT/creatinine)* • Syphilis serology* • HIV-1/2 test* • Blood for PK
	Pelvic ▲	• CVF for PK ☼ • CVF for PD ☼ • CVF for microflora ☼ • NAAT for GC/CT/TV*
	Anorectal	• Rectal fluid for PK ☼ • Rectal fluid for PD ☼ • Rectal fluid for microbiome ☼ • Rectal tissue for PK ☼ • Rectal tissue for PD ☼ • Rectal tissue for biomarkers ☼ • NAAT for GC/CT*
Study Product/Supplies		• Offer condoms

* If indicated ▲ Participants assigned female sex at birth and if anatomy allows ▼If pelvic GC/CT cannot be performed ■ Participants of childbearing potential ☼ Group 2 only

7.4.3 Other Post-Dosing Visits – Visits 5, 6, 9, and 10

The 48-hour Post-Dosing Visits (Visits 5 and 9) should occur between 44 and 52 hours (+/- 4 hours) after each dosing visit. The 72-hour Post-Dosing Visits (Visits 6 and 10) should occur between 66 and 78 hours (+/- 6 hours) after each dosing visit.

Table 14: Other Post-Dosing Visits

Other Post-Dosing Visits - Visits 5, 6, 9, and 10		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling		• HIV pre- and post-test counseling* • HIV/STI risk reduction counseling* • Protocol counseling • Behavioral In-Depth Interview (IDI) (Visit 10 only)
Clinical		• Review/update medical history • Review/update concomitant medications • Perform targeted physical examination* • Perform genital examination* • Perform pelvic examination* ▲ • Perform rectal examination • Treat or prescribe treatment for RTI/UTI, or STIs* • Provide available test results • Collect/update AEs
Laboratory	**Pharyngeal**	• NAAT for GC/CT*
	Urine	• NAAT for GC/CT* ▼ • Urine dipstick/culture* • Pregnancy test* ■
	Blood	• CBC with differential and platelets* (required at Visit 10) • Chemistries (AST/ALT/creatinine)* (required at Visit 10) • Syphilis serology* • HIV-1/2 test* (required at Visit 10) • Blood for PK
	Pelvic ▲	• CVF for PK ⌂ • CVF for PD ⌂ • NAAT for GC/CT/TV*

	Anorectal	• Rectal fluid for PK ⌂ • Rectal fluid for PD ⌂ • Rectal enema prior to biopsy collection ⌂ • Rectal tissue for PK ⌂ • Rectal tissue for PD ⌂ • NAAT for GC/CT*
Study Product/Supplies		• Offer condoms • Provide home enema kit (Visit 6 only)

* If indicated ▲ Participants assigned female sex at birth and if anatomy allows ▼If pelvic GC/CT cannot be performed ■ Participants of childbearing potential

⌂ Group 1 will have biopsies, rectal fluid and cervicovaginal fluid (if applicable) collected at 48 hours (Visits 5 and 9) following each administration of product;
Group 2 will have biopsies, rectal fluid and cervicovaginal fluid (if applicable) collected at 72 hours (Visits 6 and 10) following each administration of product.

7.4.4 Final Contact/Early Termination Visit

The *Final Contact* (Visit 11) should occur approximately 3-7 days following Visit 10 and may be conducted over the phone. This contact will also serve as the participant's study termination. Participants who permanently discontinue study product and follow-up visits prior to study completion will be asked to complete an Early Termination Visit, if willing.

Table 15: Final Contact/Early Termination Visit

Final Contact/Early Termination Visit - Visit 11		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling		• HIV pre- and post-test counseling* • HIV/STI risk reduction counseling*
Clinical		• Review/update medical history • Review/update concomitant medications • Perform targeted physical examination* • Perform genital examination* • Perform pelvic examination* ▲ • Perform rectal examination* • Treat or prescribe treatment for RTI/UTI, or STIs* • Provide available test results • Collect/update AEs
Laboratory	**Pharyngeal**	• NAAT for GC/CT*
	Urine	• NAAT for GC/CT* ▼ • Urine dipstick/culture* • Pregnancy test* ■

	Blood	• CBC with differential and platelets* • Chemistries (AST/ALT/creatinine)* • Syphilis serology* • HIV-1/2 test*
	Pelvic▲	• NAAT for GC/CT/TV*
	Anorectal	• NAAT for GC/CT*
Study Product/Supplies		• Offer condoms*

* If indicated ▲ Participants assigned female sex at birth and if anatomy allows ▼If pelvic GC/CT cannot be performed ■Participants of childbearing potential

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

7.5.1 Participants Who Become Infected with HIV-1

If a participant tests positive for HIV-1 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 to the participant, thus follow-up visits will be discontinued, study product use will cease, and the participant will be considered terminated from the study. An Early Termination Visit will occur and additional laboratory testing (including HIV RNA and HIV drug resistance testing) will be conducted for participants who have received one or more doses of study product. Please reference the MTN-039 SSP Manual for additional details (www.mtnstopshiv.org).

7.5.2 Participants Who Become Pregnant

If a participant becomes pregnant, the participant 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 product use, follow-up visits and procedures will be discontinued, and the participant will be considered terminated from the study. An Early Termination Visit will be conducted, if the participant is willing. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained, see Section 9.5 for additional details.

For participants who become pregnant while on study product, the study site will make every reasonable effort to contact participants and collect infant outcome information at approximately one year after delivery for those pregnancies that result in live birth. For additional details regarding obtaining pregnancy and infant outcomes, please reference the MTN-039 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 reason other than HIV seroconversion or pregnancy, site investigators may, after consultation with the

PSRT and MTN-039 Management Team, decide to discontinue study follow-up visits and procedures. Participants will, however, be asked to complete the procedures scheduled to occur at the Early Termination Visit (Visit 11), if willing. In the event study follow-up is continued, participants will have the protocol-specified visits through Final Contact. Sites should contact the PSRT and management team to determine whether the participant should be followed on study and what study procedures should be completed.

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

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), the participant can return for an interim visit to make up certain missed visit procedures and specimen collections. Refer to the MTN-039 SSP Manual for additional details.

All interim contacts and visits will be documented in participants' study records.

7.7 Protocol Counseling: Adherence and Contraception Counseling

At the Dosing Visit, participants will receive study product counseling appropriate to the visit. Study staff will document administration of study product and that the counseling was provided. Study product counseling will be provided to study participants upon enrollment into the study. Contraception counseling will be provided to participants of childbearing potential beginning at the Screening Visit. Protocol adherence counseling will be provided beginning at the Screening Visit. Counseling will be provided in accordance with standard study methods. Counseling also will include reminders regarding concomitant medication and behavioral restrictions prior to and following collection of biopsies.

7.8 Clinical Evaluations and Procedures

Physical Examination

The physical examination will include the following assessments:

- General appearance
- Weight*
- Vital signs
  - Temperature
  - Pulse
  - Blood pressure
  - Respirations
- Height*
- Abdomen*

- Head, Eye, Ear, Nose and Throat (HEENT) Examination*
- Oral mucosa*
- Lymph nodes*
- Neck*
- Heart*
- Lungs*
- Extremities*
- Skin*
- Neurological*
- Other components as indicated by participant symptoms

* = May be omitted after Enrollment Visit

Anorectal Examination

The anorectal examination may include the following:

- Visual exam
- Digital exam
- Anoscopy
- Flexible sigmoidoscopy

Note: Detailed information regarding the rectal and genital examination, as well as the associated procedures required for collecting specimens at each visit, can be found in the MTN-039 SSP Manual.

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

7.9 Behavioral Assessments

Participants will respond to brief computer administered self-interviews (CASI) at the Enrollment visit (Visit 2), and at the post-dose visits (Visits 4 and 8). The baseline assessment, done at Enrollment, will include, among other topics, questions on participants' prior experience and comfort using rectal products as well as douching or other rectal hygiene practices. The follow-up assessments will explore reactions to product and administration method. These assessments will allow us to identify product attributes likely to challenge and/or facilitate future sustained use when applied rectally by participants (secondary objective: acceptability). Suggestions for product improvement will also be collected.

An in-depth interview is planned at Visit 10. The in-depth interviews will include, among other topics, questions on user acceptability of the product, user-centered suggestions for product design and delivery, and experiences with the direct application method. The interview notes, recording and transcript from the in-depth interview will be considered as source documentation. Major components of these assessments to be used have been validated in prior rectal microbicide trials (e.g., MTN-006, MTN-007, MTN-017) and on-going trials (MTN-026, MTN-033, and MTN-037).

7.10 Pharmacokinetics (PK) and Pharmacodynamics (PD)

The MTN-039 cohort will provide samples for PK and PD throughout the study from Visits 2 through 10. At study randomization, participants will be assigned to one of two schedules for collection of rectal tissue (collected with flexible sigmoidoscopy), rectal fluid, and cervicovaginal fluid (if applicable):

Group 1: Visits 3, 5, 7, and 9

Group 2: Visits 4, 6, 8, and 10

Note: Both groups 1 and 2 will provide blood at Visits 3-10. At Visits 3 and 7, both groups will provide rectal fluid and cervicovaginal fluid (if applicable) – Group 1 at 2 and 6 hours post-dose, and Group 2 at 4 hours post-dose. All sampling times are approximate; allowable windows and detailed instructions are provided in the MTN-039 SSP Manual.

Table 16: Specimens to be Collected to Assess Safety, PK and *Ex Vivo* Antiviral Activity

Study Visit	Specimens collected for PK, PD and mucosal safety			
	Blood	**Rectal Fluid**	**Rectal Tissue**	**CVF**

Visit 2 - Enrollment	• Blood for PK	• RF for microbiome
		• RF for PD
			• 7 samples for biomarkers
			  ○ 1 histology
			  ○ 1 proteomics
			  ○ 1 metabolomics
			  ○ 4 flow cytometry
			• 4 samples for PD
				• CVF for microflora
				• CVF for PD

Visit 3 & Visit 7 - Samples collected at 1, 2, 4 and 6 hours	• Blood for PK	**Group 1 at 2-hour**
		• RF for microbiome
		• RF for PK
		• RF for PD
		
		Group 1 at 6-hour
		• RF for PK
		
		Group 2 at 4-hour
		• RF for PK
			Group 1 only at 2-hour
			• 7 samples for biomarkers
			• 4 samples for PD
			• 11 samples for PK
			  ○ 1 for EVG
			  ○ 1 for TFV/TFV-DP
			  ○ 1 for backup
			  ○ 8 for MMC isolation
				Group 1 at 2-hour
				• CVF for microflora
				• CVF for PK
				• CVF for PD
				
				Group 1 at 6-hour
				• CVF for PK
				
				Group 2 at 4-hour
				• CVF for PK

Visits 4 & 8 - 24 hour	• Blood for PK	**Group 2 only** • RF for microbiome • RF for PK • RF for PD	**Group 2 only** • 7 samples for biomarkers • 4 samples for PD • 11 samples for PK	**Group 2 only** • CVF for microflora • CVF for PK • CVF for PD
Visits 5 & 9 - 48 hour	• Blood for PK	**Group 1 only** • RF for PK • RF for PD	**Group 1 only** • 4 samples for PD • 11 samples for PK	**Group 1 only** • CVF for PK • CVF for PD
Visits 6 & 10 - 72 hour	• Blood for PK	**Group 2 only** • RF for PK • RF for PD	**Group 2 only** • 4 samples for PD • 11 samples for PK	**Group 2 only** • CVF for PK • CVF for PD

7.11 Laboratory Evaluations

Local Laboratory
The local laboratory will run the following, as indicated:

- Pharyngeal specimens
  - NAAT for GC/CT
- Vaginal specimens
  - NAAT for GC/CT/TV
- Urine specimens
  - hCG
  - NAAT for GC/CT
  - Dipstick/culture
- Rectal specimens
  - Rectal fluids for:
    - NAAT for GC/CT
  - Rectal tissue for:
    - PD (MTN LC approved)
- Blood specimens
  - HIV-1/2 testing, with confirmatory testing as needed
  - CBC with differential and platelets
  - Chemistries (AST/ALT/creatinine)
  - Syphilis serology
  - Coagulation (PT/INR)

Network Laboratory Center (LC)
- Cervicovaginal specimens
  - Fluid for PK (Pharmacology Core)
  - Fluid for PD (Pharmacodynamics Core)
  - Fluid for microflora
- Blood specimens
  - PK (Pharmacology Core)
  - Plasma archive
- Rectal specimens
  - Rectal fluids for:
    - PK (Pharmacology Core)
    - PD (Pharmacodynamics Core)
    - Microbiome
  - Rectal tissue for:
    - PK (Pharmacology Core)
    - Biomarkers

Once all required study analyses of collected specimens are complete, any remaining sample 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 (PTID) 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

Study sites 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-039 Study Specific Procedures Manual (http://www.mtnstopshiv.org/studies) and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to standardize procedures. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, the site is 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, 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 CDC and National Institutes of Health (NIH). All biological specimens will be transported using packaging mandated by Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

Site IoRs are responsible for continuous close safety monitoring of all study participants and for alerting the Protocol Team if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer, a CONRAD representative, and MTN Protocol Safety Physicians will serve as the PSRT. The MTN Statistical Data and Management Center (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 study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level and for alerting the PSRT if unexpected concerns arise. Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC, 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, SDMC Clinical Safety & Coding Group staff, and CONRAD representative for review.

The PSRT will meet approximately every month via conference call to review clinical data reports generated by the MTN SDMC. The content, format and frequency of the clinical data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to the routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to the MTN representing expertise in the fields of microbicides, biostatistics, HIV 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), since no Data and Safety Monitoring Board oversight is planned for MTN-039. 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 as necessary and Site IoRs will notify the responsible IRB expeditiously.

In addition to the safety monitoring, the MTN SMC will 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, and is applied to all 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 the TAF/EVG Insert, 20/16 mg.

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. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 1, 2 and 3 (Female Genital [Dated November 2007], Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies).

Please note:

- Asymptomatic BV and asymptomatic candidiasis will not be reportable AEs;
  Note: Asymptomatic BV and asymptomatic candidiasis will be captured on the CRF that captures STI results.
- Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs;
  Note: Fetal loss data will be captured on the Pregnancy Outcome CRF.

- Untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs.

Bleeding at the time of anoscope, flexible sigmoidoscope insertion/removal, and/or biopsy collection that is judged by the clinician to be within the range of what is normally anticipated will not be reportable as an AE. Bleeding of greater quantity or longer duration than what is typical, per clinician assessment, will be reportable as an AE. Fecal urgency, bloating and flatulence associated with rectal procedures deemed to be within the range of what is normally expected will not be reportable as AEs.

8.3.2 Serious Adverse Events

An SAE will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), as an AE 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 expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited adverse event (EAE) reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

DAIDS will be responsible for all FDA correspondence and for all site and DAIDS reporting. DAIDS will inform CONRAD of any reportable events and send a copy of all FDA correspondence to CONRAD. 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: Tenofovir Alafenamide (TAF)/Elvitegravir (EVG) Insert, 20/16 mg.

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 Addenda 1, 2 and 3 (Female Genital [Dated November 2007], Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies) will be used and are available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

8.4.4 Expedited AE Reporting Period

The EAE reporting period for this study begins at enrollment (i.e., randomization) 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 Infant Outcomes

Pregnant women are excluded from this study.

A participant who becomes pregnant after enrollment will continue to be followed until the end of pregnancy and, if applicable, infant outcome is ascertained, see Section 9.5 for additional details. Pregnancy and infant outcomes will be reported on relevant CRFs. Pregnancy outcomes will not be expeditiously reported to CONRAD or the DAIDS Medical Officer (MO) unless there is an associated AE in the pregnant participant that meets expedited reporting criteria or the pregnancy results in a congenital anomaly meeting the Manual for Expedited Reporting of EAEs to DAIDS (Version 2.0, January 2010) guidelines for expedited reporting.

8.6 Regulatory Requirements

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

8.7 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. 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 permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to permanently discontinue study product use at any time if he/she feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. IoRs/designees will document all permanent discontinuations on applicable CRFs.

9.1 Grading System

AE severity grading is described in Section 8.4.3.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

9.3 General Criteria for Permanent Discontinuation of Study Product

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

- Acquisition of HIV infection; for those who acquire HIV, study product should be held beginning immediately upon recognition of the first positive/reactive HIV test
- Pregnancy or breastfeeding
- Anogenital STIs
- 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.
- Reported use of or need for PrEP or PEP. Participants who experience a known or potential HIV exposure during study participation or have a recognized risk of exposure and thus need PEP or PrEP will have study product permanently discontinued and will be referred for PEP or PrEP initiation. Those who need PEP will be encouraged to start it as quickly as possible and within 72 hours of potential exposure. Since continued study follow-up would be of no benefit following permanent discontinuation of study product use, these participants will be exited from the study.
- Anticoagulant use (e.g., heparin, Lovenox, warfarin and Plavix)
- Use of certain CYP3A inhibitors and inducers (as specified in Table 8 and Table 9)
- Participant develops a Grade 4 adverse event.

9.4 Follow-up in Response to Observed Adverse Events

Grade 1 and Grade 2 Unrelated
In general, a participant who develops a Grade 1 AE, regardless of relationship to study product, may continue product use. Participants who develop a Grade 2 AE that is judged by the IoR/designee to be unrelated to study product may also continue product use. If the IoR/designee opts to temporarily hold study product, the PSRT must be notified.

Grade 2 Related and Grade 3
For participants who develop a Grade 2 AE that is judged by the IoR/designee to be related to product or any Grade 3 AE, study product must be held and the IoR must consult with PSRT regarding provision of the second dose.

Grade 4
For participants who develop a Grade 4 AE study product must be permanently discontinued and the PSRT notified.

9.5 Pregnancy

Female participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The IoR/designee will counsel any participant who becomes pregnant regarding possible risks to the fetus according to site SOPs. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

A participant who becomes pregnant during study participation will have study product discontinued and will be terminated from the study, as per Section 7.5.2. 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. 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).

9.6 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. IoRs/designees 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 (see details regarding the Early Termination Visit in Section 7). Study staff members will record the reason(s) for all withdrawals in participants' study records.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and General Design

MTN-039 is a phase 1, open label, single-arm, two-period trial designed to characterize the safety and PK profiles of the TAF/EVG Insert, 20/16 mg administered rectally at two dose levels (one insert in the first period and two inserts in the second period). Twenty HIV-uninfected individuals 18 years of age or older will receive a single dose (one insert), then allow time for adequate washout before application of the two-insert dose. Samples will be taken over a 3-day period after each dose application.

10.2 Study Endpoints

Primary Endpoints

Consistent with the primary study objectives to (1) evaluate the safety of the TAF/EVG Insert when applied rectally at two dose levels and (2) characterize the systemic and rectal pharmacokinetics of the TAF/EVG Insert(s) following rectal application, the following endpoints will be assessed:

- **Safety**
  All Grade 2 and higher AEs

- **Pharmacokinetics**
  EVG concentrations in:
  - Blood
  - Rectal fluid
  - Rectal mucosal tissue homogenates

  TAF and TFV concentrations in:
  - Blood
  - Rectal fluid

  TFV-DP concentrations in:
  - Rectal mucosal tissue homogenates
  - Rectal mucosal tissue cell isolates

10.3 Primary Study Hypotheses

MTN-039 hypothesizes that TAF and EVG will be safe when applied to the rectum and well-tolerated among healthy men and women who have a history of receptive anal intercourse (RAI).

10.4 Sample Size and Power Calculations

Safety Endpoints

The proposed total sample size for assessing safety is approximately N=20 participants. This sample size is based upon the size of similar Phase 1 studies of microbicides for HIV prevention.

As a means to characterize the statistical properties of this study, Table 17 below presents the probability of observing zero, at least one, and two or more safety endpoints among the 20 participants for various "true" event rates:

Table 17: Analysis of Safety Event Frequency

Event Rate	P (0 events | n=20)	P (≥1 event | n=20)	P (≥2 events | n=20)
1%	81.8	18.2	1.7

5%	35.8	64.2	26.5
10%	12.2	87.8	60.8
15%	3.9	96.1	82.4
20%	1.2	98.8	93.0
25%	0.3	99.7	97.6

If the true rate of a safety endpoint is 5%, the probability of observing that endpoint in at least one out of 20 participants is 0.64.

An alternative way of describing the statistical properties of the study design is in terms of the 95% confidence interval for the true rate based on the observed data. Table 18 below shows the exact 2-sided 95% confidence intervals for the probability of an event based on a particular observed rate. If none of the 20 participants receiving a particular dose (one insert or two inserts) experience a safety event, then the 95% exact 2-sided upper confidence bound for the true rate of such events for that dose is 16.8%.

Table 18: Exact 2-sided 95% Confidence Intervals Based on Observing a Particular Rate of Safety Endpoints among 20 Participants

Observed event rate	Confidence interval (%)
0/20 (0%)	0.0, 16.8
1/20 (5%)	0.1, 24.9
2/20 (10%)	1.2, 31.7
3/20 (15%)	3.2, 37.9

Additional participants may enroll in the study, at the discretion of the protocol team, to replace currently enrolled participants lost to follow-up or to permanent product discontinuation. Thus, if additional participants are recruited for this purpose, the total sample size at the end of the study may slightly exceed 20 participants who received either dose of TAF and EVG.

10.5 Randomization Procedures

There will be no randomization to dose of TAF and EVG (one insert or two inserts) in this open-label, single-arm, and two-period trial. However, upon enrollment, participants will be randomly assigned to one of two sample collection schedules for the collection of rectal tissue (collected with flexible sigmoidoscopy), rectal fluid, and cervicovaginal fluid (if applicable):

Group 1: Visits 3, 5, 7, and 9

Group 2: Visits 4, 6, 8, and 10

Note: Both groups 1 and 2 will provide blood at Visits 3-10. At Visits 3 and 7, both groups will provide rectal fluid and cervicovaginal fluid (if applicable) – Group 1 at 2 and 6 hours post-dose, and Group 2 at 4 hours post-dose.

Randomization will be stratified by sex at birth to incorporate at least three participants assigned female sex at birth in each group.

The randomization scheme will be generated and maintained by the MTN SDMC.

10.6 Participant Accrual, Follow-up and Retention

Based on previous studies of rectal products with similar eligibility requirements, the accrual of approximately 20 eligible participants will take approximately 6-8 months. Individuals lost to follow-up or to permanent product discontinuation may be replaced after statistical and team input have been received. However, every effort will be made to complete the regularly scheduled safety evaluations and retain all enrolled participants in follow-up to minimize possible bias associated with loss-to-follow-up.

10.7 Data and Safety Monitoring and Analysis

10.7.1 Study Monitoring Committee

No Data and Safety Monitoring Board oversight is planned for this study. The MTN SMC will conduct interim reviews of participant safety data and 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 this review, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

10.7.2 Primary Analysis

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

Safety Endpoints

All visits in which a participant 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. The number and the percentages of participants experiencing each safety endpoint (see Section 10.2) will be tabulated by dose (one insert or two inserts). Each participant will contribute once in each category (i.e., only for highest severity AE for each participant) for the calculation of event rates for each dose.

To assess the overall tolerability of the two doses (one insert or two inserts), participants in each dose may be compared for characteristics including safety events and laboratory measurements using descriptive statistics. Due to the small sample size, formal comparisons will not be done.

Pharmacokinetic Analysis

We will use descriptive statistics for continuous variables as defined above to describe the EVG and tenofovir-related analyte (TAF, TFV) concentrations in blood, rectal fluid, and rectal tissue assessed at all scheduled time points. For each dose (one insert or two

inserts), the 1 to 72-hour time points will be used to describe the concentrations beginning soon after a dose exposure through time to peak concentrations through initial elimination among different matrices. EVG developmental PK studies are planned to be conducted in parallel with this study to inform interpretation of EVG tissue PK and explant results.

10.7.3 Secondary and Exploratory Analyses

Acceptability Analysis
We will use descriptive statistics to summarize overall acceptability of the two dose regimens and to identify product attributes considered likely to challenge and/or facilitate future sustained use of the TAF/EVG Insert when applied rectally.

Pharmacokinetic/Pharmacodynamic Analysis
We will use descriptive statistics for continuous variables as defined above to describe the EVG and tenofovir-related analyte (TAF, TFV) concentrations in cervicovaginal fluid at all scheduled time points. For each dose (one insert or two inserts), the 1 to 72-hour time points will be used to describe the concentrations beginning soon after a dose exposure through time to peak concentrations through initial elimination in cervicovaginal fluid.

Ex vivo HIV explant data will use virus levels to compare baseline levels with virus levels on study product. Concentration-response relationships may also be explored using appropriate linear and non-linear models. Rectal fluid and cervicovaginal fluid will be assessed for anti-HIV activity, and the percent inhibition will be correlated to EVG and tenofovir-related analyte (TAF, TFV) concentrations.

10.7.4 Missing Data

Every effort will be made to complete the regularly scheduled safety and PK evaluations and retain all enrolled participants in follow-up over the two dose evaluations lasting approximately 21 to 77 days total, including washout. Based on previous MTN trials, we expect to have minimal missing data. If participants are lost to follow-up or to permanent product discontinuation, they may be replaced, as mentioned above. If missing data rates are higher than anticipated (over 15%) for a particular dose safety evaluation or for individual pharmacokinetic measure time points, then additional participants may enroll in the study at the discretion of the protocol team.

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 reports and queries will be 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 must identify all CRFs to be used as source documents. Study CRF data will be entered into the MTN-039 database, transferred in compliance with the

US-EU Safe Harbor Requirements and the EU Data Protection Directive 95/46/EC to the MTN SDMC, entered, and cleaned using Medidata Rave, a data management system compliant with the International Council on Harmonization (ICH) Good Clinical Practices (GCP) and US CFR guidelines for electronic data capture.

Transcriptions of interviews will be generated using the audio files recorded at University of Pennsylvania. Both the audio files and the transcripts will be uploaded and managed using a qualitative software package. Interview notes will be kept at the University of Pennsylvania in the participant files.

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, for the investigational products tested, IoRs/designees will maintain all study documentation for at least two years following the date of marketing approval for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US FDA is notified.

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

11.3 Quality Control and Quality Assurance

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 will visit study 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 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

IoRs/designees 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. IoRs/designees also will allow inspection of all study-related documentation by authorized representatives of the MTN LOC, SDMC, LC, CONRAD, NIAID, FDA, OHRP, IRBs, and other local, US or international regulatory authorities. A site visit log will be maintained at study sites to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, IoRs/designees will have obtained IRB approval and the protocol will have been submitted to the FDA. IoRs/designees 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

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

After 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 (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, sites must have the protocol and the protocol consent forms approved, as appropriate, by its local IRB 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 RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

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

Upon receiving final IRB 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 site 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 all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement (CTA) executed by NIAID and CONRAD.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chair and DAIDS Medical Officer. Study implementation will also be guided by a common Study-Specific Procedures (SSP) Manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to 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 and documentation. 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.

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

Pharyngeal Swab
Pharyngeal (throat) swab collection often causes a momentary gagging reflex.

Rectal Enema
An enema is a standard procedure that may be used prior to insertion of a flexible sigmoidoscope since fecal matter can obscure the test. The main risk from having an enema is temporary discomfort. A hollow tube about the thickness of a pencil will be used to put approximately 120 mL of normal saline 0.9% into the rectum and flush it out again (a larger volume may be required if the initial volume does not produce results), along with any stool that is there. There is a risk of a bloated/cramping feeling. The tube is small, but it might cause some anal or rectal discomfort if the participant has any hemorrhoids or other painful conditions. There is also a remote possibility of rectal perforation associated with the use of an enema.

Finger and Anoscope Rectal Exams
During rectal exams and collection of rectal fluid and tissue samples, insertion of a finger or lubricated anoscope will likely cause some discomfort.

Flexible Sigmoidoscopy and Rectal Biopsy Collection
Flexible sigmoidoscopy is a commonly practiced endoscopic medical procedure and will not involve any increased risk over usual sigmoidoscopy performed for clinical indications. There is a low risk of infection, mild rectal irritation, low blood pressure, and feeling a sudden urge to defecate during or after the flexible sigmoidoscopy procedure. There is a very low risk of an intestinal tear during the flexible sigmoidoscopy procedure.

There is a risk of limited rectal bleeding 1-2 days after flexible sigmoidoscopy, associated with collection of biopsy samples. The rate of perforation of a hollow viscus following endoscopic biopsy occurs less than 88 out of every 100,000 times.[32] A recent retrospective analysis of approximately 1,000 research flexible sigmoidoscopies (including collection of rectal biopsies) conducted at the University of Pittsburgh demonstrated an overall adverse event rate of 1.6%. The majority of AEs were gastrointestinal in nature and of mild/moderate severity.[33]

Participants will be instructed to refrain from sexual intercourse and counseled not to use aspirin (over 81 mg per day) and non-steroidal anti-inflammatory drugs (NSAIDS) within

72 hours prior to and following a tissue sample collection visit. 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 or if the participant develops any abnormal odor or discharge from the rectum.

Rectal Fluid Collection

There is the risk of mild discomfort in addition to a slight risk of bleeding with the insertion of rectal swabs and sponges for collection of rectal fluid.

Other Risks

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

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

Sexual partner notification in response to diagnosed STI or HIV infection could cause problems in participants' relationships. Participants also could have problems in their partner relationships associated with study-required abstinence.

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

Risks Associated With EVG Insert[8]

If administered rectally, an insert containing EVG may cause the following:

- Rectal urgency
- Rectal irritation
- Rash
- Exacerbation of hemorrhoid symptoms

Risks Associated With Oral EVG[7]

These risks are based on the safety assessment of EVG oral tablets when co-administered with other ARVs:

Most Common Adverse Reactions (All grades, incidence ≥10%) in subjects receiving EVG were:

- Headache
- Diarrhea

- Nausea
- Fatigue

Other Common Adverse Reactions (All grades, incidence ≥1% and <10%) were:
- Depression
- Insomnia
- Abdominal pain
- Vomiting
- Dyspepsia
- Rash

Uncommon Adverse Reactions (All grades, incidence ≥0.1% and <1%) in patients with a pre-existing history of depression or psychiatric illness were:
- Depression
- Insomnia
- Suicidal ideation and suicide attempt

Risks Associated With TAF[12]
These risks are based on the safety assessment of TAF oral tablets from previous randomized, double-blind, active-controlled trials:

Most Common Adverse Reactions (All grades, incidence ≥5%) were:
- Headache
- Abdominal pain
- Cough
- Back pain
- Fatigue
- Nausea
- Arthralgia
- Diarrhea
- Dyspepsia

Other Common Adverse Reactions (All grades, incidence ≥1% and <5%) were:
- Vomiting
- Rash
- Flatulence

There is a theoretical risk of the development of HIV drug resistance to tenofovir or elvitegravir if the participant acquires HIV infection around the time of study drug administration.

Risks Associated With Rectally-Applied Drugs
In previously completed studies involving repeated use of rectally-applied gel products, the following AEs were observed. These side effects may or may not be associated with the use of TAF/EVG Insert administered rectally:

More Common Adverse Reactions (incidence ≥5%) were:

- Flatulence
- Defecation urgency
- Diarrhea

Less Common Adverse Reactions (incidence <5%) were:

- Abdominal distension
- Abdominal bloating
- Abdominal pain/cramps
- Tenesmus
- Irritation in the rectum
- Rash
- Worsening of existing problems due to hemorrhoids

13.4.2 Benefits

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

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical and rectal examination, and routine laboratory testing related to blood, liver, and kidney function. Participants may be provided or referred for STI treatment free of charge, and STI testing and treatment may be offered and/or referrals may be provided (for their partners). For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals.

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to screening. Written informed consent also will be obtained for long-term specimen storage and possible future testing, although consent for long-term specimen storage is not required for study participation. In obtaining and documenting informed consent, IoRs 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 ICF if they are willing to receive them.

In addition to the ICF, 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 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 study product
- The need to abstain from sexual intercourse for protocol defined periods
- The importance of participants in all 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. Study sites 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.

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, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored securely. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' identification numbers to identifying information will be stored in a locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

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

The MTN has a Certificate of Confidentiality from the US Department of Health and Human Services that is applicable to 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 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 and time away from work. Site specific reimbursement amounts will be specified in the site specific ICF.

13.9 Communicable Disease Reporting

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

13.10 Access to HIV-related Care

13.10.1 HIV Counseling and Testing

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV-1 screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV-1/2 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 sites and additionally will emphasize the unknown efficacy of the study products in preventing HIV-1 infection. In accordance with the policies of the NIH, participants must receive their HIV-1/2 test results to take part in this study.

13.11 Study Discontinuation

This study may be discontinued at any time by NIAID, the MTN, CONRAD, the US FDA, the OHRP, other government or 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. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS, NIAID, and NIMH for review prior to submission.

15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

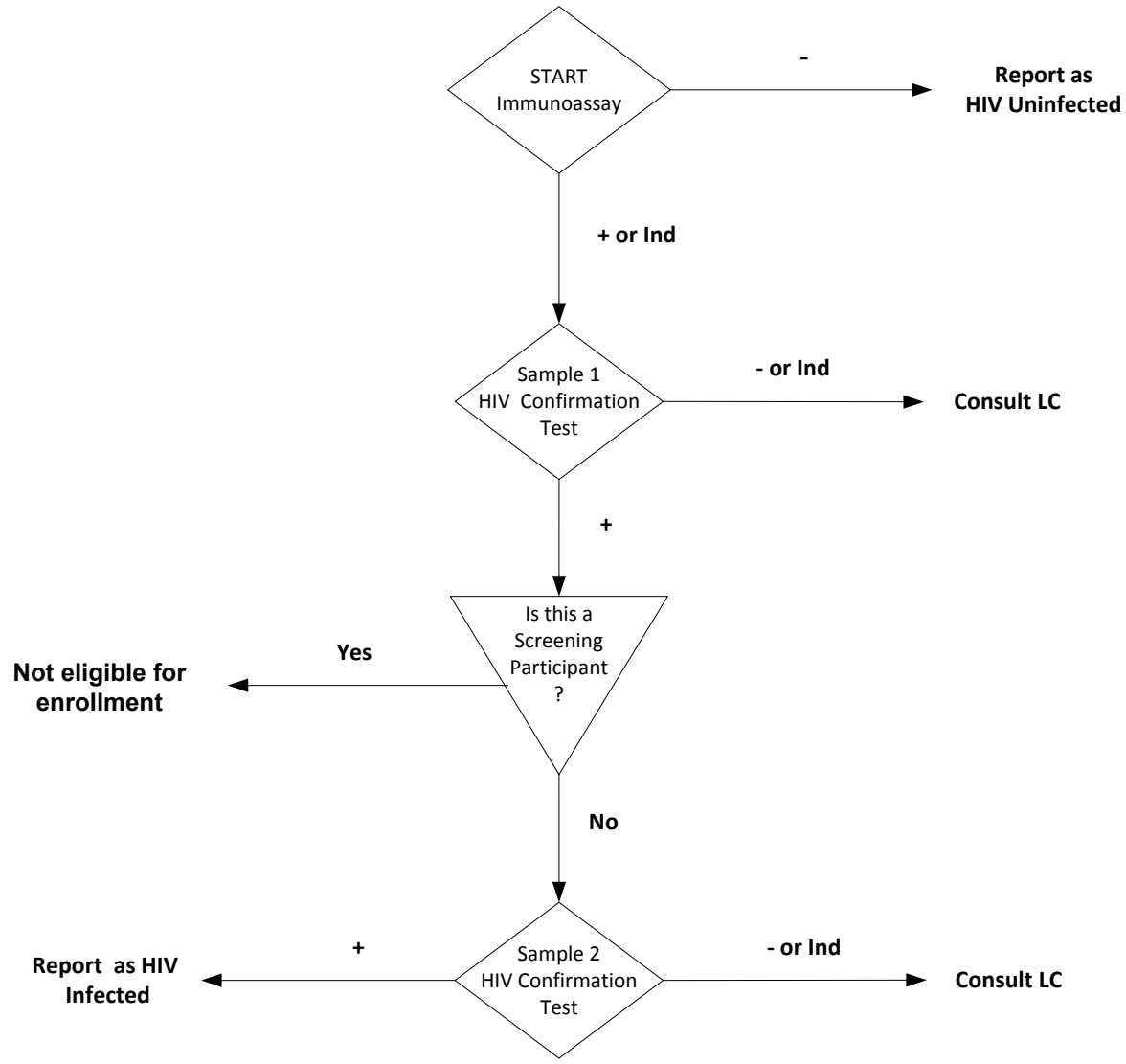
	Screening Visit 1	**Enrollment** Visit 2 (Day 0)	**Dosing** Visits 3, 7	**24 hours Post-Dosing** Visits 4 and 8	**Other Post-Dosing** Visits 5, 6, 9, and 10	**Final Contact/Early Termination** Visit 11
ADMINISTRATIVE AND REGULATORY						
Obtain written informed consent	X					
Assign a unique Participant Identification (PTID) number	X					
Assess and/or confirm eligibility	X	X				
Collect demographic information	X					
Collect/review/update locator information	X	X	X	X	X	X
Random assignment of sampling schedule		X				
Provide reimbursement	X	X	X	X	X	X
Schedule next visit/contact	*	*	X	X	X	*
BEHAVIORAL/COUNSELING						
HIV pre- and post-test counseling	X	X	*	*	*	*
HIV/STI risk reduction counseling	X	X	*	*	*	*
Protocol counseling	X	X	X	X	X	
Behavioral assessment (CASI)		X				
Behavioral assessment (Brief CASIs)				X		
Behavioral IDI					X (Visit 10)	
CLINICAL						
Collect/review/update concomitant medications	X	X	X	X	X	X
Collect/review/update medical history	X	X	X	X	X	X
Perform physical exam (Targeted at Visits 3-10)	X	X	*	*	*	*
Perform genital exam	*	*	*	*	*	*
Perform pelvic exam ▲	*	*	*	*	*	*
Perform rectal exam	X	X	X	X	X	*
Treat or prescribe treatment for RTI/UTI/STIs	*	*	*	*	*	*
Provide available test results	X	X	X	X	X	X
Collect/update AEs			X	X	X	X
LABORATORY						
PHARYGEAL — NAAT for GC/CT	X	*	*	*	*	*
URINE — NAAT for GC/CT▼	X	*	*	*	*	*
URINE — Pregnancy test ■	X	X	*	*	*	*
URINE — Urine dipstick/culture	*	*	*	*	*	*

		Screening Visit 1	**Enrollment** Visit 2 (Day 0)	**Dosing** Visits 3, 7	**24 hours Post-Dosing** Visits 4 and 8	**Other Post-Dosing** Visits 5, 6, 9, and 10	**Final Contact/Early Termination** Visit 11
BLOOD	CBC with differential and platelets	X	*	*	*	* (required at visit 10)	*
	Chemistries (AST/ALT/creatinine)	X	*	*	*	* (required at Visit 10)	*
	Syphilis serology	X	*	*	*	*	*
	Coagulation (PT/INR)	X					
	Plasma for archive		X				
	HIV-1/2 test	X	X	*	*	* (required at Visit 10)	*
	Blood for PK		X	X ♦	X	X	
PELVIC ▲	NAAT for GC/CT/TV	X	*	*	*	*	*
	CVF for PK			X **	☼	X ⌂	
	CVF for PD		X	♣ (2 hrs post-dose)	☼	X ⌂	
	CVF for microflora		X	♣ (2 hrs post-dose)	☼		
ANORECTAL	NAAT for GC/CT	X	*	*	*	*	*
	Rectal fluid for PK			X **	☼	X ⌂	
	Rectal fluid for PD		X	♣ (2 hrs post-dose)	☼	X ⌂	
	Rectal fluid for microbiome		X	♣ (2 hrs post-dose)	☼		
	Rectal enema prior to biopsy collection		X			X ⌂	
	Rectal tissue for PK			♣ (2 hrs post-dose)	☼	X ⌂	
	Rectal tissue for PD		X	♣ (2 hrs post-dose)	☼	X ⌂	
	Rectal tissue for biomarkers		X	♣ (2 hrs post-dose)	☼		
STUDY PRODUCT SUPPLY							
Administration of study product				X			
Offer condoms		X	X	X	X	X	*
Offer lubricant				X			
Provide home enema kit			X			X (Visit 6 only)	

* If indicated
▲Participants assigned female sex at birth and if anatomy allows
▼If pelvic GC/CT cannot be performed
■ Participants of childbearing potential
♦ All participants will have blood collected at 1, 2, 4, and 6 hours following product administration

	Screening Visit 1	**Enrollment** Visit 2 (Day 0)	**Dosing** Visits 3, 7	**24 hours Post-Dosing** Visits 4 and 8	**Other Post-Dosing** Visits 5, 6, 9, and 10	**Final Contact/Early Termination** Visit 11
⌂ Group 1 will have biopsies, rectal fluid and cervicovaginal fluid (if applicable) at 48 hours (Visits 5 and 9) following each administration of product; Group 2 will have biopsies, rectal fluid and cervicovaginal fluid (if applicable) collected at 72 hours (Visits 6 and 10) following each administration of product. ♣ Group 1 only ☼ Group 2 only ** Group 1: 2 and 6 hours post-dose; Group 2: 4 hours post-dose Note: All sampling times are approximate; allowable windows are provided in the MTN-039 SSP manual.						

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



Ind: Indeterminate test results
LC: Laboratory Center

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

DIVISION OF AIDS, NIAID, NIH

MTN-039
Version 1.0
March 6, 2019

A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels

PRINCIPAL INVESTIGATOR: *[Site to insert]*
PHONE: *[Site to insert]*
Short Title for the Study: Safety and PK Study of TAF/EVG Administered Rectally

INFORMED CONSENT

IMPORTANT INFORMATION ABOUT THE RESEARCH STUDY

You are being asked to take part in this research study because you are a healthy, HIV-negative adult, 18 years of age or older and reported at least one experience of consensual receptive anal sex in your lifetime. Approximately 20 people will participate in this study at two sites in the United States. National Institute of Health's Division of AIDS (DAIDS) is the sponsor of this Microbicide Trials Network (MTN) study. At this site, the person in charge of this study is ***[INSERT NAME OF PRINCIPAL INVESTIGATOR]***.

Important things you should know:

- The study product in this clinical trial is an insert that contains tenofovir alafenamide (TAF) and elvitegravir (EVG). The insert resembles a tablet and dissolves quickly once inside the body. It contains 20 mg TAF and 16 mg EVG. Both drugs are used to treat HIV and are now being tested to see if they also prevent HIV.
- The purposes of this study are:
    - To find out if it is safe to apply the TAF/EVG Insert in the rectum.
    - To better understand the way the body absorbs, distributes, and gets rid of TAF and EVG when the insert is used in the rectum.
    - To understand whether you find it acceptable to use the insert when applied to the rectum.
- If you qualify and choose to participate, you will receive two doses of the TAF/EVG Insert, 20/16 mg. The first dose will be one insert and the second dose will be two inserts. After each dose, you will have laboratory tests and clinical evaluations or exams for research purposes and to make sure you do not have any side effects. The second dose will be administered 7-49 days (1-7 weeks) after the first one. You will be randomly assigned to one of two sampling schedules for the lab tests.

- You will be asked to attend 10 clinic visits at this study clinic and will be followed for approximately 6-13 weeks. The total length of your participation in this study will be about 4 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 rectal exam will be performed;
    - Blood will be obtained to test for HIV and/or other sexually transmitted infections (STI) and for research purposes;
    - Urine will be collected to test for infections and (if applicable) pregnancy;
    - Rectal and vaginal fluids will be collected for research purposes and to test for STIs (if applicable). At 5 of the 10 visits, rectal tissue will also be collected;
    - You will be asked to complete 3 short interviews and a longer interview at Visit 10.
- Some common side effects from the use of TAF and/or EVG in oral forms include: headache, diarrhea, nausea, fatigue, abdominal pain, cough, back pain, vomiting and rash. Uncommon adverse reactions include depression, insomnia and suicidal thoughts and attempts in patients with a history of depression or psychiatric illness.
- There are no direct benefits for taking part 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 and STI testing, physical and rectal examinations, and routine laboratory testing.
- 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 this study, 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. You may decide to stop being in the study at any time.

What is the study product?

Elvitegravir (EVG) is an anti-HIV medication that is FDA approved for oral use in combination with other medications for the treatment of HIV. EVG works in a specific way to potentially prevent HIV from making copies of itself, thereby stopping the spread of HIV in the human body.

Oral EVG has been tested in combination with other medications in large clinical studies for treatment of HIV infection. These studies have shown that EVG in combination with other drugs is generally safe, with the most frequently reported adverse events being

related to the stomach and intestines. EVG in the form of an insert has been tested in animals in the vagina and in the rectum for drug absorption and safety with no findings of concern.

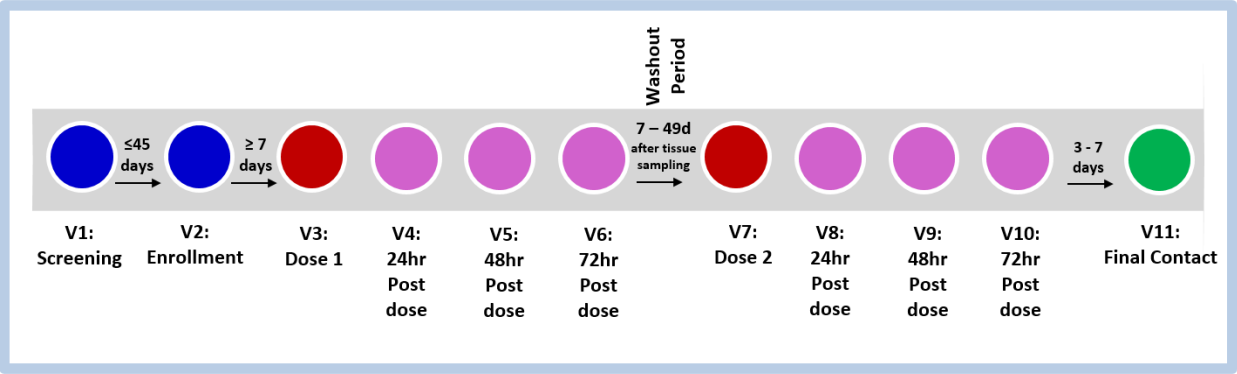
Tenofovir alafenamide (TAF) is a medication that is FDA approved for the treatment of chronic hepatitis B or in combination with other medications for the treatment of HIV. TAF also inhibits the replication of HIV virus, therefore stopping the spread of HIV in the human body.

TAF has been tested in clinical studies for safety and efficacy alone and as part of combination therapy that includes EVG. Similarly, study results indicated that TAF taken alone or in combination with other anti-HIV medications is generally safe.

Researchers now would like to learn about the safety of the TAF/EVG Insert applied rectally and how the body absorbs, distributes, and gets rid of TAF and EVG. In this study, TAF and EVG are being tested for the first time in humans as a rectally-applied insert.

Who will be in this research study and what will I be asked to do if I join?
The study includes a total of 10 clinic visits and one final contact, including the Screening Visit which is taking place today. All clinical visits will take place at this study clinic.

Study Visit Schedule



Screening Visit:

The procedures done today will take about ***[SITES TO INSERT TIME]***. Multiple visits may be conducted to complete all required screening procedures.

You will:

- Answer questions to confirm you are able and willing to join the study
- Answer questions about where you live, your medical history, including what medications you are taking
- Provide study staff your contact information (i.e. where you live and how we can contact you)

- Be asked to abstain from some medications during your participation in the study:
  - Blood thinners
  - Non-study related rectally-administered medications and any products containing N-9
  - Certain medications that might interact with TAF or EVG
  - Medications used for PrEP (oral Truvada® or other PrEP) or PEP (post-exposure prophylaxis). However, if you need medication due to a known or potential exposure to HIV, you should take it but let the study staff know as soon as possible
- Talk with study staff about sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex
- Have a physical exam
- If applicable, have your urine or vaginal fluid collected (via a swab) to test for sexually-transmitted diseases and other infections
- Provide a blood sample ***[SITES TO INSERT AMOUNT]***:
  - To test the health of your blood, liver and kidneys
  - To test for infections that typically are passed through sex, including HIV and syphilis
    - 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 sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we are sure of your status. To participate in the study, you must 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.
- Have a throat swab (like a Q-tip) collected, to test for infections passed through sex
- Have a rectal examination. Rectal fluid will be collected with a swab; these will be used to test for sexually transmitted infections (STIs). To examine the rectum, study staff will insert a short hollow tube called an anoscope. The clinician will insert the swab through the hollow tube to collect the sample.
- If applicable:
  - Your urine will be tested for pregnancy
    - If you are pregnant you cannot join this study
    - Staff will discuss with you ways to avoid getting pregnant
- Be treated or referred for treatment of sexually transmitted infections, and/or be referred for any other care if needed
- Receive your test results, when available. It is expected that all of your results will be available by ***[SITES TO SPECIFY TIMEFRAME]***.
- Be offered male condoms
- Be compensated for your visit
- Schedule your next visit to enroll in the study, if you are willing and eligible.

You will be asked to abstain from the following activities at timepoints specified during the study:

Activity:	*Abstain For How Long?*

• Receptive intercourse
  ○ Anal
  ○ Oral
• Receptive anal or genital stimulation (e.g., fingers, partner placing their mouth on your anal or genital area)
• Inserting any non-study products or objects into your rectum, including:
  ○ Fingers
  ○ Rectal medications
  ○ Enemas
  ○ Lubricants
  ○ Sex toys (dildos, anal plugs, etc.)
	• 72 hours (3 days) prior to each clinic visit
	• 72 hours (3 days) following each clinic visit

• Receptive vaginal intercourse
• Inserting non-study products or objects into your vagina, including:
  ○ Fingers
  ○ Spermicides
  ○ Vaginal medications (including hormones)
  ○ Vaginal douches
  ○ Lubricants
  ○ Vaginal moisturizers
  ○ Sex toys (vibrators, dildos, etc.)
	• 72 hours (3 days) prior to each clinic visit

• Using aspirin (greater than 81 mg) and non-steroidal anti-inflammatory drugs (NSAIDS)	• 72 hours (3 days) prior to tissue sample collection visit • 72 hours (3 days) following tissue sample collection visit

If you do not think you can be sexually abstinent for the required length of time before and after study visits, you should not join this study.

If you decide not to join this study, blood and other samples collected at this visit will not be kept or used for any tests other than those listed above.

Enrollment Visit:

Your Enrollment Visit (the visit where you enter the study) will take about ***[SITES TO INSERT TIME.]***

The following procedures are specific to the Enrollment Visit, which will take place up to 45 days after your Screening Visit.

You will:

- Answer questions to confirm you are able and willing to join the study
- Update your contact information
- Be assigned to a study sample collection sequence
    - You will be assigned to one of two groups for timing of sample collection (rectal fluid and vaginal fluid [if applicable] and rectal tissue) by random chance (like a roll of the dice). Neither you nor the study staff can control which group you will be assigned to.
    - At some of your study visits after the Enrollment Visit, these samples may be collected at approximately 2, 4, and/or 6 hours after receiving the TAF/EVG Insert(s), and approximately 24, 48, or 72 hours later, depending on the timing of sample collection you have been assigned to. This table shows the different times when each group has samples collected:

Visit	Post-Dose Hours	Rectal Tissue		Rectal Fluid		Vaginal fluid	
		Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Dosing Visits (Visits 3 and 7)	2	X		X		X	
	4				X		X
	6			X		X	
24-hour Post-Dosing Visits (Visits 4 and 8)	24		X		X		X
48-hour Post-Dosing Visits (Visits 5 and 9)	48	X		X		X	
72-hour Post-Dosing Visits (Visits 6 and 10)	72		X		X		X

    - You will be able to find out today at which visit(s) you will have these samples collected and how long each study visit will last.
    - These samples will help researchers learn how the body absorbs, distributes, and gets rid of TAF and EVG.

- Talk with study staff about the following:
    - The instructions and procedures of the study and how to follow the study guidelines, including the sexual abstinence requirement and use of non-study products/objects.
    - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex
- Discuss any health problems you may have had in the past or since your last visit (including what medications you are taking)
- Discuss with study staff the initiation of any new medication, over the counter drug or food supplement product (vitamins, nutritional supplements and herbal preparations).
- Complete a brief computer-administered self-interview (CASI). This will take approximately 20-30 minutes. You will be asked some questions about your experience and comfort in using rectal products, as well as douching or other rectal hygiene practices, among other things.
- Provide a blood sample ***[SITES TO INSERT AMOUNT]***:
    - In case there's a question about your test results at a later time
    - To test your blood for HIV, the virus that causes AIDS
    - To see if there is study drug in your body prior to the use of study product
- Have a physical exam
- In preparation for the rectal sample collection, you will have an enema.
    - During an enema, a hollow tube about the thickness of a pencil will be used to put some saline solution (salt water) through your anus and squeeze it into your rectum to flush it out and cleanse the bowel of fecal matter (stool). An enema is standard procedure prior to insertion of a flexible sigmoidoscope, since fecal matter can obscure the test. This may need to be repeated so that any stool that is there is removed
- Have a rectal exam where rectal fluid and tissue samples will be collected.
    - To collect rectal fluid samples: Study staff or the clinician will insert a short hollow tube called an anoscope inside your rectum and insert swabs and/or sponges through the hollow tube to collect the sample.
    - To collect rectal tissue samples: A flexible sigmoidoscopy will be performed.
        - A flexible sigmoidoscope is a flexible, hollow tube that is placed inside your rectum so that the study clinician can take samples of tissue.
        - The study clinician will collect approximately 11 tissue samples, each about the size of a grain of rice
- If applicable:
    - Have a urine test for pregnancy and discuss with study staff ways to avoid getting pregnant
    - Have a swab inserted in the vagina to collect fluid for research purposes
- Be given test results, if available
- Be given male condoms, if you need them

- Be given a home enema kit. Study staff will tell you how to use the kit at home the evening prior to Dosing Visit 3.
- Be reimbursed for your visit
- Schedule your next visit, if applicable.

Dosing Visits (Visits 3 and 7):

All participants will receive a single TAF/EVG Insert at Visit 3, and two TAF/EVG Inserts at Visit 7, administered by study staff. Visits 3 and 7 will take approximately ***[SITES TO INSERT AMOUNT OF TIME]***.
You will:

- Update your contact information
- Review the instructions and procedures of the study and how to follow the guidelines, including about sexual abstinence and insertion of non-study products or objects
- Discuss any health problems you may have had since your last visit (including what medications you are taking)
- Have study insert(s) administered by study staff
- Have blood samples collected ***[SITES TO INSERT AMOUNT]***
    - At approximately 1 hour, 2 hours, 4 hours, and 6 hours after each dose
    - An intravenous cannula (IV tube) may be placed for up to 6 hours after administration of the insert(s) for the blood draws. These samples will be collected to help researchers better understand how the study drug is processed by the body.
- Have a rectal examination and have rectal fluid and tissue collected using the anoscope and flexible sigmoidoscope
    - For Group 1 participants, both rectal fluid and tissue samples will be collected at 2 hours after each dose of study insert(s) and only rectal fluid will be collected at 6 hours after each dose of study insert(s). At 2 hours, the study clinician will also collect approximately 22 tissue samples, each about the size of a grain of rice
    - For Group 2 participants, only rectal fluid sample will be collected at 4 hours after each dose of study insert(s).
- If applicable:
    - Have vaginal fluid collected with a swab
    - For Group 1 participants, vaginal fluid sample will be collected at 2 hours and 6 hours after each dose of study insert(s).
    - For Group 2 participants, vaginal fluid sample will be collected at 4 hours after each dose of study insert(s).
- Discuss with study staff about any problems that you may be experiencing as a result of administration of the study insert(s), or as a result of procedures performed during your visit
- Be provided with any available test results and with treatment or a referral for treatment if your test results indicate that you require it

- Be given male condoms, if you need them
- Be reimbursed for your visit
- Schedule your next visit or contact.

24-Hour Post-Dosing Visits (Visits 4 and 8):

You will be asked to attend a 24-Hour Post-Dosing Visit (Visits 4 and 8) approximately 24 hours (1 day) after each dosing visit. Each visit will take between ***[SITES TO SPECIFY TIMEFRAME]*** to complete.
At these visits, you will:

- Update your contact information
- Review the instructions and procedures of the study and how to follow the guidelines, including about sexual abstinence and insertion of non-study products or objects
- Discuss any health problems you may have had since your last visit (including what medications you are taking)
- Complete a brief computer-administered self-interview. This interview may take approximately 10 -15 minutes. You will be asked questions about your thoughts on the study product, what might make the product more appealing to use and your experience with the insert administration in the clinic.
- Have a rectal examination and have rectal fluid and tissue collected using the anoscope and flexible sigmoidoscope (Group 2 participants only). The study clinician will collect approximately 22 tissue samples, each about the size of a grain of rice.
- If applicable (Group 2 participants only)
    - Provide a small amount of vaginal fluid via swab for research purposes
- Provide a blood sample ***[SITES TO INSERT AMOUNT]***:
    - To help researchers to better understand how the body absorbs, distributes, and gets rid of the study drug
- Speak with study staff about any problems that you may be experiencing as a result of administration of the study insert(s), or as a result of procedures performed during your visit
- Be given any available test results
- Be given condoms, if you need them
- Be reimbursed for your visit
- Schedule your next visit or contact.

48-Hour Post-Dosing Visits (Visits 5 and 9):

You will be asked to attend a 48-Hour Post-Dosing Visit (Visits 5 and 9) approximately 48 hours (2 days) after each dosing visit. Each visit will take between ***[SITES TO SPECIFY TIMEFRAME]*** to complete.

At these visits, you will:

- Update your contact information
- Talk with study staff about the instructions and procedures of the study and how to follow the guidelines, including about sexual abstinence and insertion of non-study products or objects
- Discuss any health problems you may have had since your last visit (including what medications you are taking)
- Have a rectal examination and have rectal fluid and tissue collected using the anoscope and flexible sigmoidoscope (Group 1 participants only)
    - In preparation for the tissue collection you will have an enema (rectal lavage).
    - The study clinician will collect approximately 15 tissue samples, each about the size of a grain of rice.
- If applicable (Group 1 participants only)
    - Provide a small amount of vaginal fluid via swab for research purposes
- Provide a blood sample ***[SITES TO INSERT AMOUNT]***:
    - To help researchers to better understand how the study drug is processed by the body
- Discuss with study staff about any problems that you may be experiencing as a result of administration of the study insert(s), or as a result of procedures performed during your visit
- Be given any available test results
- Be given condoms, if you need them
- Be reimbursed for your visit
- Schedule your next visit or contact.

72-Hour Post-Dosing Visits (Visits 6 and 10)

You will be asked to attend a 72-Hour Post-Dosing Visit (Visits 6 and 10) approximately 72 hours (3 days) after each dosing visit. Each visit will take between ***[SITES TO SPECIFY TIMEFRAME]*** to complete.

At these visits, you will:

- Update your contact information
- Talk with study staff about the instructions and procedures of the study and how to follow the guidelines, including about sexual abstinence and insertion of non-study products or objects
- Discuss any health problems you may have had since your last visit (including what medications you are taking)
- Have an in-depth interview (at Visit 10 only). This interview may take approximately 30 - 45 minutes. You will be asked questions about your thoughts on the study product, if the product is acceptable to you, what might make the product more appealing to use and your experience with the insert administration in the clinic, among other topics. This conversation 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 made up names, and the hardware will be physically protected in a locked area. This means that no one other than the 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-039 study team for the purposes of this research.

- Have a rectal examination and have rectal fluid and tissue collected using the anoscope and flexible sigmoidoscope (Group 2 participants only)
    - In preparation for the tissue collection you will have an enema (rectal lavage).
    - The study clinician will collect approximately 15 tissue samples, each about the size of a grain of rice.
- If applicable (Group 2 participants only)
    - Provide a small amount of vaginal fluid via swab for research purposes
- Provide a blood sample ***[SITES TO INSERT AMOUNT]***:
    - To test the health of your blood, liver and kidneys (Visit 10 only)
    - To test your blood for HIV, the virus that causes AIDS (Visit 10 only)
    - To help researchers to better understand how the body absorbs, distributes, and gets rid of the study drug
- Discuss with study staff about any problems that you may be experiencing as a result of administration of the study insert(s), or as a result of procedures performed during your visit
- Be given any available test results
- Be given condoms, if you need them
- Be given a home enema kit at Visit 6. Study staff will tell you how to use the kit at home the evening prior to Dosing Visit 7.
- Be reimbursed for your visit
- Schedule your next visit or contact.

Final Contact (Visit 11)

Your Final Contact will take place approximately 3-7 days following Visit 10. This visit/contact will take approximately ***[SITES TO SPECIFY TIMEFRAME]*** to complete and can be conducted over the phone.

At this visit, you will:

- Update your contact information
- Discuss any health problems you may have had since your last visit (including what medications you are taking)
- Discuss any problems that you may be experiencing as a result of using the study insert(s) or as a result of procedures performed during the study
- Be reimbursed for your visit, if required
- Schedule your next visit or contact (if necessary)
- Be given any available test results

- Be given male condoms, if you need them.

It is important that you remember that at any time during the study, study staff can answer any questions you may have about the procedures mentioned above or any other aspect of this study.

Other Procedures
In addition to the procedures listed above, it is possible that study clinicians may need to perform additional tests, if necessary (e.g., if you report having symptoms of a urinary, genital, or other infection and/or other issues). These tests might include the following:

- Physical exam
- Pelvic exam
- Genital exam
- Rectal exam
- Test rectal or throat samples for STIs
- Test cervix/vaginal samples for STIs
- Test your urine for STIs or other infections
- Test your blood for STIs
- Test your blood to check the health of your blood, liver and kidneys
- Give you treatment or refer you for treatment of STIs or other issues, if needed.

Further you may need to provide additional samples if any of the above procedures need to be repeated due to issues with sample processing, and/or testing or shipping. Additional testing may be performed as part of quality control.

What are the possible risks, side effects, and discomforts of this research study?
It is not expected that participation into this study will expose you to unreasonable risks.

Risks from study drug
The following side effects have been associated with the use of EVG in participants in other studies in which the drug was taken by mouth. These side effects may or may not be associated with the use of EVG when the drug is taken rectally:

<u>Most Common Adverse Reactions</u> occurring in 10% or more of participants receiving EVG by mouth:

- Headache
- Diarrhea
- Nausea
- Tiredness

Other Common Adverse Reactions occurring in between 1% and 10% of participants receiving EVG by mouth:

- Depression
- Inability to sleep
- Pain in abdomen
- Vomiting
- Indigestion
- Rash

Uncommon Adverse Reactions occurring in between 0.1% and <1% of participants receiving EVG by mouth:

- Depression
- Inability to sleep
- Suicidal thoughts and suicide attempt in patients with a history of depression or psychiatric illness

The following side effects have been associated with the use of TAF in participants in other studies in which the drug was taken by mouth. These side effects may or may not be associated with the use of TAF when the drug is taken rectally:

Most Common Adverse Reactions occurring in 5% or more of participants receiving TAF:

- Headache
- Abdominal pain
- Cough
- Back pain
- Fatigue
- Nausea
- Joint pain
- Diarrhea
- Dyspepsia

Other Common Adverse Reactions occurring in between 1% and 5% of participants receiving TAF:

- Vomiting
- Rash
- Flatulence

There is a theoretical risk of the development of HIV drug resistance to tenofovir or elvitegravir if the participant acquires HIV infection around the time of study drug administration.

It is also possible that you may have an allergic reaction to the study product. Signs of allergic reaction may include: rash, dizziness, itching, muscle aches, nausea, fainting, facial flushing, chest tightness, cough, hives, fever, and shortness of breath.

Risks from rectally-applied drugs
The following side effects have been associated with the repeated use of rectally-applied gel in other studies. These side effects may or may not be associated with the use of TAF/EVG Insert administered rectally:

More Common Adverse Reactions occurring in 5% or more of participants:
- Passing gas from the intestinal tract
- A sudden, almost uncontrollable, need to relieve the bowels
- Diarrhea (loose, frequent stools)

Less Common Adverse Reactions occurring in less than 5% of participants:
- Abdominal bloating, feeling full, or a sense of abdominal pressure and/or pain
- Feeling a constant need to pass stools, despite an empty bowel
- Irritation in the rectum
- Rash
- Worsening of existing problems due to hemorrhoids

Risks from phlebotomy and IV cannula placement (blood tests)
- You may feel discomfort.
- You may feel dizzy or faint.
- You may have a bruise, swelling, small clot, or infection where the needle goes in your arm.
- You may have excessive bleeding.

Risks of throat swab
- A throat swab often causes a momentary gagging reflex.

Risks of enemas
- The main risk from having an enema is temporary discomfort. A hollow plastic tube about the thickness of a pencil will be used to administer about 120-125 mL of enema fluid into the rectum.
- You may experience some mild discomfort and a bloated or “crampy” feeling.
- If you have any hemorrhoids or other painful conditions, you might feel anal or rectal discomfort.
- There is also a remote possibility of rectal perforation associated with the use of an enema.

Risks of finger and anoscope rectal exams
- During rectal exams and collection of rectal fluid and tissue samples, insertion of a finger or lubricated anoscope will likely cause mild discomfort.

Risks of rectal swab/sponge insertion

- Insertion of rectal swabs and sponges may cause mild discomfort, in addition to a slight risk of bleeding.

Risks of flexible sigmoidoscopy

- A flexible sigmoidoscopy is a commonly practiced medical procedure where a flexible tube with a small camera attached is used to look inside the rectum and lower colon. The procedures done in this study will not involve any increased risk over usual flexible sigmoidoscopy performed for clinical indications (for routine medical diagnosis or treatment).
- The risks associated with these procedures include mild discomfort, a sudden urge to relieve the bowels, the feeling of having a "bloated stomach", low blood pressure, light bleeding following a bowel movement, abnormal odor or discharge from the rectum, as well as flatulence (gas passed through the anus/rectum) following the procedure.

Risks of endoscopic biopsy

- Endoscopic biopsies (biopsies done using a slender, lighted optical tube) to collect rectal tissue samples are painless and heal quickly within 3 days.
- On extremely rare occasions, the endoscopic procedure or biopsies may lead to pain, infection (sepsis), bleeding or perforation (small hole or tear) of the stomach or intestines. Perforation occurs less than once out of every 1,000 procedures (88/100,000 procedures). If this extremely rare complication occurs, antibiotics and surgery to repair the tear may be necessary.
- If you engage in sexual intercourse before the biopsy has healed, there exists the risk of temporary discomfort, and increased risk of STIs and HIV infection.

(If applicable) Risks of vaginal swab

- During vaginal fluid collection, you may feel discomfort or pressure in your vagina or genital area.

Other Possible Risks:

- You may become embarrassed and/or worried when discussing your sexual practices, ways to protect against HIV and other infections passed through sex, and your test results.
- You may feel anxious while waiting for your test results, and after receiving them. Trained study counselors will help you deal with any feelings or questions you have.
- Finding out your HIV status could cause depression and/or suicidal thoughts. It could also cause problems between you and your partner(s). If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.
- It is possible that you and/or your partner(s) may experience problems in your relationship(s) associated with maintenance of the study-required abstinence.

- It is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.
- The interviews that take place at some of your clinic visits will be computer-administered and questions of a personal nature may be asked. Responding to these questions may make you uncomfortable. You may choose not to answer any question that makes you uncomfortable.

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. Any names that might be mentioned during the interview will NOT be retained. Instead a generic description will be used in the records (i.e., if you refer to a friend's name, "FRIEND1" will be noted).

What are possible benefits from taking part in this study?

- There are no direct benefits for taking part in this study, but you or others may have future benefit from information learned in this study. You may also learn more about HIV and other diseases and ways to protect yourself from infection.
- It is important that you know that you will not be paid any additional money (beyond the reimbursement described below for study participation) if the study product being studied is eventually licensed for use.
- You will have physical and rectal exams. You will also have tests to check the overall health of your liver, kidneys, and blood cells. If these tests show that you might have any health problems, you will be told about medical care and other services available to you. This will be available to you even if you do not enroll in this study. This study cannot provide you with general medical care, but study staff will refer you to other available sources of care.
- You will get counseling and testing for HIV and STIs. If you have infections passed through sex, other than HIV infection, you will be offered medicine to treat them or provided information for where you may receive treatment, and study staff will discuss options available for counseling and treatment of your partner. This treatment or referral for treatment is available to you even if you do not enroll in this study.
- If you become infected with HIV, you will need to receive care from your own health care provider or we will provide you with a referral. This study does not provide medication for treatment of HIV/AIDS.
- You will receive free male condoms, if you need them.

Will this study product prevent HIV infection?

We do not know if the drugs contained within the insert work to protect men and women from getting HIV. This study is <u>not</u> testing to see if TAF/EVG Insert prevents HIV infection. Researchers are continuing to study TAF and EVG to learn more about how they work in humans to protect against HIV infection. There are two known effective ways to reduce your risk of contracting HIV: the use of condoms and/or the use of oral pre-exposure prophylaxis (PrEP) medication, Truvada®, or post-exposure prophylaxis (PEP). PrEP is

an HIV prevention method in which 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 and PEP if you are interested in learning more. If you are interested in these alternative options, you may also want to discuss them with your doctor. If you are currently taking PrEP or PEP or plan to take PrEP in the near future, you will not be eligible for this study.

What if there is new information learned during this study?
We will tell you about new information from this or other studies that may affect your willingness to stay in this study. You will also be told when study results may be available, and how to learn about them.

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.

Is it possible that I may be taken out of the study without my consent?
A study clinician may need to remove you from the study early without your permission if:

- The study is cancelled by the US FDA, US NIH, CONRAD (the organization that supplies the rectal insert), the US Office for Human Research Protections (OHRP), MTN, the local or other government or 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. A SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study.
- You are found to be infected with HIV (see "If You Become Infected With HIV" section below) or an STI in your anal or genital area.
- (Females) You become pregnant or are breastfeeding (see "If You Become Pregnant" section below).
- If you start on medication for PEP or PrEP
- You report the use of the following prohibited medications:
    - Anticoagulants (e.g., heparin, Lovenox, warfarin and Plavix)
    - Certain CYP3A inhibitors or inducers (e.g., grapefruit, Prozac, Zoloft, Prednisone, Prilosec)
- A study clinician decides that using the study would be harmful to you, for example you have a bad reaction to the study insert(s).
- Other reasons that may prevent you from completing the study successfully, such as you are not able to reliably keep appointments.

If You Become Infected With HIV
Your participation in this study will not cause HIV infection. However, there is always a chance that through sexual activity or other activities (e.g., needle sharing for recreational drug use) you may become infected with HIV. In the unlikely event

that you become infected with HIV, study staff will give you counseling and refer you to available medical care and other services you may need. The study does not pay for this care. Tests will be performed to see if you have HIV drug resistance. This will allow your doctor to know what HIV drugs would be best for the treatment of your type of HIV. If the HIV test shows that you have been infected with HIV, you will stop using the study insert. You may be referred to other research studies. Continued study participation would be of no added benefit to you, so your participation in the study will be discontinued.

(If applicable) If You Become Pregnant

The study insert is not a birth control method. You must agree to use an effective method of birth control such as birth control pills or another hormonal-based method, or an intrauterine device (IUD), unless you or your partner have been sterilized (i.e., no longer able to become pregnant), and/or you only have sex that cannot lead to pregnancy (no penile-vaginal intercourse). You should use an effective method of contraception at least 30 days prior to enrollment or abstain from penile-vaginal intercourse 90 days prior to enrollment.

We do not know what effect TAF/EVG Insert has on pregnancy, including its effect on the fetuses of women who use the rectal insert when pregnant, or the babies of women who use the insert when breastfeeding. Because of this, pregnant women and women who are breastfeeding may not join this study. Women who join this study will have pregnancy tests while in the study.

If you become pregnant during the study, study staff will refer you to available medical care and other services you or your baby may need. The study does not pay for this care. You will stop using the insert and you will exit the study. We will contact you to find out about your pregnancy and the outcome of your pregnancy. The outcome of your pregnancy is important to study staff; therefore, your pregnancy will be followed until the results of your pregnancy are known. 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.

If you are removed from or choose to leave this study, you will be asked to complete the procedures described for Visit 11, if you are willing to do so. The study clinician will ask you to stop using the study insert but continue to come in for follow-up visits and procedures if you have a bad reaction to the insert.

Will there be any payments if I take part in this research study?

[SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT:] You will receive [***SITES TO INSERT AMOUNT*** **$**] for your time, effort, and travel to and from the clinic at each scheduled visit. You may receive [***SITES TO INSERT AMOUNT*** **$**] for any visits which occur in between your normally scheduled visits.

What are the costs?
[SITES TO COMPLETE ACCORDING TO SITE CAPACITY] There is no cost to you for study related visits, physical/rectal examinations, laboratory tests or other procedures. Treatments available to you from the study site for infections passed through sex will be given to you free of charge or you will be referred for available treatment for the duration of the study.

Are there any other studies if I cannot join this one?
There may be other studies going on at this study clinic or in the community for which you may be eligible. If you wish, we will tell you about other studies that we know about. There may also be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish. If you choose not to take part in this study, it will have no effect on the regular medical care available to you at this clinic or elsewhere.

Who will know about my participation in this research study?
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. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names. *[Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/IECs:* All original study documents that provide information about you for this study will be kept for at least two years after either the study insert is approved for use or research on the insert is stopped.]

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

Your records may be reviewed by:
- Study staff
- Site Institutional Review Boards
- PPD (a contract research organization that monitors clinical trials for safety and data quality)
- Representatives of CONRAD, the nonprofit organization that supplies the study rectal insert
- Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH
- Other local, US and international regulatory authorities.

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

[Sites to include/amend the following:]
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. With limited exceptions, researchers may not disclose names, information or documents containing information you give for study purposes. This Certificate does not expire.

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. Also, we may have to release your information if the organization that is funding this study, [*Funding Agency*], requests the information, or if the FDA, EMA or other regulatory body tells us to release this information. This Certificate does not prevent you from releasing information about yourself and your participation in the study.

What if I am injured as a result of participating in this study?
[SITES TO SPECIFY INSTITUTIONAL POLICY:] It is unlikely that you will be injured as a result of study participation. If you are injured, the ***[institution]*** will give you immediate necessary treatment for your injuries. You ***[will/will not]*** have to pay for this treatment. You will be told where you can receive additional treatment for your injuries. The U.S. National Institutes of Health (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.

May I withdraw my consent for participation in this research study?
[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, nor will the confidentiality of the care provided for you here be affected. You should feel free coming back to this facility even if you decide not to participate in this study. If you want the results of the study after the study is over, let the study staff members know.

What do I do if I have questions?

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

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

CONSENT FOR LONG-TERM STORAGE AND FUTURE TESTING OF SPECIMENS

There might be a small amount of blood, rectal tissue, rectal fluid, or vaginal fluid left over after we have done all of 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. The de-identified data and specimens could then be used for future research by our research team or other researchers without notifying you or asking your permission for this use. Your biospecimens will never be used for commercial profit.

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 or sequencing (for example, the mapping of all of your genes, also known as whole genome sequencing) is planned for leftover samples 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 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. 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
_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

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