MTN-011

Phase 1 Evaluation of the Impact of Coitus on the Pharmacokinetics and Pharmacodynamics of Tenofovir 1% Gel Following Pericoital or Daily Gel Dosing

Microbicide Trials Network

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine transaminase
APV	amprenavir
ARV	antiretroviral
ASCCP	American Society for Colposcopy and Cervical Pathology
AST	aspartate aminotransferase
AUC	area under the curve
BAT	Before sex, a dose After sex, and not more than Two applications
BID	twice daily
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
BV	bacterial vaginosis
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CASI	Computer-Assisted Self Interviewing
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CORE	Coordinating and Operations Center
CRF	case report form
CRS	Clinical Research Site
CROI	Conference on Retroviruses and Opportunistic Infections
CT	*Chlamydia trachomatis,* chlamydia
CTA	Clinical Trial Agreement
CV	coefficient of variation
CVL	cervicovaginal lavage
CWG	Community Working Group
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAIDS PRO	DAIDS Protocol Registration Office
DAPY	di-amino-pyrimidine
DC	drug concentration
DLV	delavirdine
DNA	deoxyribonucleic acid
DSC	differential scanning calorimetry
EAE	Expedited Adverse Event
EFV	efavirenz
FDA	(US) Food and Drug Administration
FDR	false discovery rate
FHCRC	Fred Hutchinson Cancer Research Center
FTC	emtricitabine
g	grams
GALT	gut-associated lymphoid tissues
GC	*Neisseria gonorrhoeae,* gonorrhea
GCP	Good Clinical Practices

GEE	Generalized Estimating Equations
GMP	good manufacturing practices
HAART	highly active antiretroviral therapy
hCG	human Chorionic Gonadotropin
HEC	hydroxyethylcellulose
HEENT	Head, Eyes, Ears, Nose, and Throat
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HPV	human papillomavirus
HSV	herpes simplex virus
IATA	International Air Transport Association
ICF	informed consent form
IDV	indinavir
IND	investigational new drug
IoR	Investigator of Record
IRB	Institutional Review Board
IUD	intrauterine device
KOH	potassium hydroxide
kg	kilogram
LLN	lower limit of normal
LLOQ	lower limit of quantification
µg	microgram
mg	milligram
mL	milliliter
MO	Medical Officer
MTD	maximum tolerated dose
MTN	Microbicide Trials Network
NAAT	Nucleic Acid Amplification Test
NFV	nelfinavir
ng	nanogram
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NL	network laboratory
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no-observed-adverse-effect-level
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OBT	optimized background therapy
OHRP	Office for Human Research Protections
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PEP	post-exposure prophylaxis
PI	protease inhibitor
PK	pharmacokinetics
PMPA	9-[9(R)-2-(phosphonomethoxy)propyl]adenine
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development, Inc.
PSRT	Protocol Safety Review Team
PTID	participant identification
QD	once daily
RNA	ribonucleic acid
RSC	Regulatory Support Center
RE	Regulatory Entity
RT	reverse transcriptase
RTI	reproductive tract infection

SAE	serious adverse event
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SMS	Short Message Service
SOP	standard operating procedure
SQV	saquinavir
SSP	study specific protocol
STD	sexually transmitted disease
STI	sexually transmitted infection
SUSARs	Suspected, unexpected serious adverse reactions
TEAE	treatment-emergent adverse events
TFV	tenofovir
UA	urinalysis
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
UPLC	ultra performance liquid chromatography
USA	United States of America
UTI	urinary tract infection
WHO	World Health Organization
wt	wild-type
w/w	weight/weight
ZDV	zidovudine

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INVESTIGATOR SIGNATURE FORM

Version 1.0

April 24, 2012

A Study of the Microbicide Trials Network

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

IND Holder:
CONRAD

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

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

_____
Name of Investigator of Record

_____ _____
Signature of Investigator of Record Date

MTN-011

Phase 1 Evaluation of the Impact of Coitus on Pharmacokinetics and Pharmacodynamics of Tenofovir 1% Gel Following Pericoital or Daily Gel Dosing

PROTOCOL SUMMARY

Short Title: Coital PK/PD of Tenofovir Gel

Clinical Phase: Phase 1

IND Sponsor: CONRAD

Protocol Chair: Betsy Herold, MD

Sample Size: Approximately 40 couples

Study Population: Heterosexual sexually active monogamous couples, in which both individuals are healthy and HIV-negative. The female participants must be between the ages of 21-46 (inclusive) and currently using effective non-barrier contraception. Male participants must be 21 years of age or older.

Study Site: Site(s) selected by the MTN Executive Committee

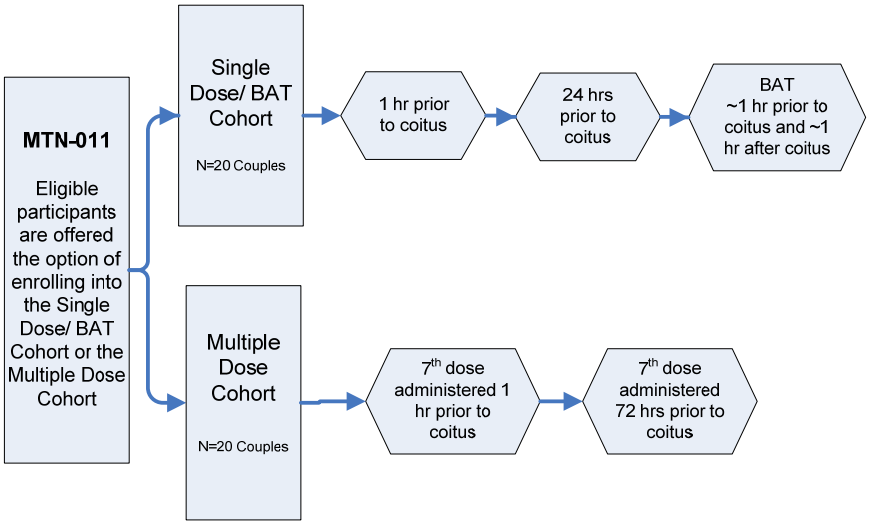
Study Design: Phase 1, multi-site, non-randomized, multi-sequence, open-label study

Study Duration: Approximately 6-12 months for planned accrual and study duration

- Group 1- Single Dose /BAT Cohort: approximately 8 weeks (~2 menstrual cycles) on study
- Group 2- Multiple Dose Cohort: approximately 14 weeks (~3 menstrual cycles) on study

Study Regimen: Female participants will receive tenofovir 1% gel

Figure 1: Study Groups



Primary Objectives:

Pharmacokinetics

1. To assess the impact of coitus (and semen) on the pharmacokinetics of tenofovir 1% gel in female genital tract secretions, vaginal and cervical tissue and rectal tract secretions

Pharmacodynamics

2. To assess the impact of coitus (and semen) on pharmacodynamics of luminal drug by measuring the anti-HIV-1 activity in CVL samples

Primary Endpoints:

Pharmacokinetics

1. Tenofovir and tenofovir diphosphate levels
   - Cervicovaginal lavage
   - Cervical cytobrush
   - Vaginal and cervical biopsies
   - Blood
   - Rectal sponge

Pharmacodynamics

2. Anti-HIV-1 activity in CVL

Secondary Objective:

Acceptability

1. To assess the acceptability of the MTN-011 trial to male and female participants

Secondary Endpoints:

Acceptability

1. Overall experience with participating in the clinical trial
2. Willingness to participate in a future trial

Exploratory Objectives:

Impact of coitus and/or tenofovir

1. To determine impact of coitus and/or tenofovir on the genital tract mucosal environment
2. To determine whether a semen biomarker can be used to estimate the volume of ejaculate within CVL
3. To assess whether sufficient drug is retained in the lumen in the absence of or following coitus to inhibit HSV-2 as an additional surrogate biomarker of pharmacodynamics

Exploratory Endpoints:

Impact of coitus and/or tenofovir

1. Measurement of biomarkers of mucosal immunity
2. Measurement of semen biomarker in ejaculate and in CVL
3. Anti-HSV-2 activity in CVL

Table 1: Group 1 Study Visit Schedule

Group 1- Single Dose/BAT Cohort				
Gel	**Visit**	**Visit Name**	**Targeted Visit Schedule**	**Coitus**
	1 ♂♀	Screening		
	2a ♂♀	Enrollment/ No Gel/ Coitus	To occur ~2-3 days after the final day of the female's last period*	X
	2b♀	Post-Coital Sampling	To occur ~2 hrs after coitus	
-1 hr	3a ♂♀	Gel -1/Coitus	To occur ~3-7 days after Visit 2	X
	3b♀	Post-Coital Sampling	To occur ~2 hrs after coitus	
	4a ♀	Gel -1/No Coitus	To occur after a min.10-day washout period	
	4b ♀	Sampling	See Visit 3b for details	
-24 hr	5a ♂♀	Gel -24/Coitus	To occur after a min.10-day washout period	X
	5b ♀	Post-Coital Sampling	To occur ~2 hrs after coitus	
	6a ♀	Gel -24/No Coitus	To occur after a min.10-day washout period	
	6b ♀	Sampling	See Visit 5b for details	
BAT	7a ♂♀	Gel -1/Coitus/ Gel +1	To occur after a min.10-day washout period	X
	7b/ Final ♂♀	Post-Coital Sampling	To occur ~2 hrs after coitus	

♀= female ♂= male, * scheduling guidance for participants who are amenorrhoeic can be found in the SSP Manual

Table 2: Group 2 Study Visit Schedule

Group 2- Multiple Dose Cohort				
Gel	**Visit**	**Visit Name**	**Targeted Visit Schedule**	**Coitus**
	1 ♂♀	Screening (Baseline CVL)		
	2 ♂♀	Enrollment- Provision of Study Product	To occur ~2-3 days following the final day of the female participant's period*	
-1 hr	3a ♂♀	Gel -1/Coitus	To occur 6 days after Visit 2	X
	3b ♀	Post-Coital Sampling	To occur ~2 hrs after coitus	
	4 ♀	Provision of Study Product	To occur after a min. 20 day washout period	
	5 ♀	Sampling	To occur at similar time relative to sampling at Visit 3b	
-72 hr	6 ♀	Provision of Study Product	To occur after a min. 20 day washout period	
	7a ♂♀	Gel -72/Coitus	To occur 9 days after Visit 6	X
	7b ♀	Post-Coital Sampling	To occur ~2 hrs after coitus	
	8 ♀	Provision of Study Product	To occur after a min. 20 day washout period	
	9/ Final ♂♀	Sampling	To occur at similar time relative to sampling at Visit 7b	

♀= female ♂= male * scheduling guidance for participants who are amenorrhoeic can be found in the SSP Manual

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Phase 1 Evaluation of the Impact of Coitus on Pharmacokinetics and Pharmacodynamics of Tenofovir 1% Gel Following Pericoital or Daily Gel Dosing
Protocol Number:	MTN-011
Short Title:	Coital PK/PD of Tenofovir Gel
Date:	April 24, 2012

1.2 Sponsor and Monitor Identification

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2 INTRODUCTION

The recently announced results of CAPRISA 004 represent a groundbreaking step in HIV prevention research.[1] This double-blind, randomized controlled trial compared the use of tenofovir 1% gel versus placebo gel (coitally-dependent regimen) in 889 sexually active women in South Africa. Tenofovir gel reduced HIV acquisition by an estimated 39% overall (p=0.017). When the results were examined in subgroups by adherence, the reduction of HIV acquisition in the group who reported greater than 80% adherence was 54%, whereas the reduction in the group who reported less than 50% adherence was 28%. Further research on the safety and effectiveness of tenofovir 1% gel will be required before drug regulatory authorities would consider licensure of tenofovir gel as an approved product for prevention of HIV in women. While these efficacy data are promising, additional data are still necessary. Recently, the daily dosing regimen of tenofovir 1% gel used in the ongoing MTN-003 (VOICE) Phase 2B effectiveness study was not shown to be associated with reduced rates of HIV acquisition and the VOICE Data Safety Monitoring Board (DSMB) recommended that this arm of the VOICE study be stopped for futility. These results require additional data to examine the role of sex, semen, and timing of gel administration to understand the role these variables play on the pharmacokinetics (PK) or pharmacodynamics (PD) of tenofovir 1% gel.

The Microbicide Trials Network (MTN) Study MTN-011 will contribute to HIV prevention research by providing currently unavailable information regarding the impact of coitus on PK and PD of tenofovir 1% gel.

2.1 Rationale

Microbicide gels may be applied either daily or in a coitally-dependent manner and each has distinct advantages for different populations. Women who have more frequent intercourse may prefer a daily gel regimen whereas women with infrequent intercourse may prefer a coitally-dependent regimen. However, the frequency and timing of sex relative to drug application may play an important role by modifying the PK and biodistribution, thus impacting drug efficacy. For example, a woman who applies gel infrequently and shortly prior to sex may lose a substantial fraction of the dose from leakage or dilution and thus not be fully protected. In contrast, sex and semen may have less impact on drug PK and PD in the setting of daily or more frequent gel application. The timing and frequency of dosing may have contributed to the variability in protection observed in the CAPRISA 004 study, in which women were instructed to apply a first dose of gel within 12 hours before anticipated sexual intercourse and a second dose as soon as possible after intercourse, with no more than 2 doses in a 24 hour period (BAT24). Notably, the majority of women reported applying the first dose within 1 hour of intercourse and their second dose within 1 hour of intercourse.[3]

In an effort to help to explain the varying efficacy results, MTN-011 participants will alter the application and timing of their gel doses relative to sex. By simulating what researchers hypothesize VOICE and CAPRISA participants may have done, they will be better equipped to understand whether the timing of gel application relative to sex and

the physical act of sex may have impacted the PK and PD of tenofovir. By understanding some of the variables that impact PK/PD, the team will help to inform the field and may provide insight into the differing results between CAPRISA and VOICE.

A recently completed post-coital study of PRO 2000/5 gel (P), demonstrates the importance of post-coital sampling in understanding potential efficacy.[4,5] The study was an open-label study conducted among 10 monogamous couples to determine the concentration of drug and antiviral activity in cervicovaginal lavage (CVL) obtained after intravaginal application of a single dose of 0.5% PRO 2000/5 gel (P) in the absence of, or following, penile-vaginal intercourse. Results showed a significant loss in the antiviral activity in genital tract secretions collected by CVL following barrier-unprotected sex compared to the protective activity measured in CVL collected following gel application in the absence of sex. Furthermore, less PRO 2000/5 gel (P) was recovered in post-coital CVL, suggesting that the physical act of sex resulted in the redistribution of gel and/or leakage.[5] These studies illustrate that post-coital measurements differ from pre-coital measures and thus highlight the need for post-coital PK/PD studies.

MTN-011 will build from this experience to assess tenofovir PK in the genital tract secretions (CVL), rectal (rectal sponge) and both intracellular and extracellular tissue compartments (vaginal and cervical biopsies) in the absence of, or following coitus. Pharmacodynamics (antiviral activity) will also be assessed in CVL. The goal is to better understand the variability in drug PK/PD in the setting of coitus. Group 1 will examine PK/PD following a single dose of gel applied 1 hour prior, 24 hours prior, or 1 hour before and 1 hour after (BAT) sex, the dosing regimen used most by women in CAPRISA 004; Group 2 will examine PK/PD following seven daily doses of gel with the last dose applied 1 hour or 72 hours prior to sex. The single or BAT dosing regimens will provide drug PK/PD data in the absence of any tissue reservoir as might have occurred in CAPRISA 004. The multiple dosing arms will provide PK/PD data when a reservoir is present (7 daily doses) and explore how long that reservoir persists (last dose applied 1 vs. 72 hours prior to sex/sampling), which may help to inform the results of VOICE.

The results of this comparison can only be fully understood if both variables (sex and gel) are controlled for. Thus, controls will include dosing and sampling in the absence of sex (both Groups) or in the absence of gel (Group 1 only). In all cases, clinical samples will be obtained ~2 hours after sex or a matched timepoint (no sex). Mucosal secretions have “endogenous” antiviral activity, which likely reflects the cumulative effects of antimicrobial peptides, pH, and other mucosal mediators. The physical act of intercourse may alter this activity, reflecting contributions from semen and/or its impact on the female genital tract. Thus, CVL obtained at the Screening visit (no gel/no sex) and the Enrollment Visit, where no gel will be applied, but sex will occur,) for Group 1 participants will provide baseline data in the absence of any gel product (See Section 7 for additional details). If tenofovir retains its antiviral activity following sex, then the anti-HIV activity in the CVL sample collected at the Gel/Sex Visit should be comparable to that of a sample collected at the Gel/No Sex Visit and should be greater than that of the sample collected at the visits without gel dosing (No Gel/No Sex, No Gel/Sex visits).

This unique design allows each participant to serve as their own control for these comparisons.

We hypothesize that coitus and semen may not have the same impact on PK/PD in the setting of daily gel application due to continual accumulation of drug in cervicovaginal tissue over time. Thus Group 2 will compare PK/PD after 7 daily doses of gel in the absence of sex to that of the PK/PD after the couple engages in sex. While the 7-day dosing regimen is insufficient to establish steady-state tenofovir diphosphate concentrations for all women in cells and tissue (intracellular median half-life [interquartile range] 61 (49-112 hours in peripheral blood mononuclear cells [PBMC], possibly shorter in tissue)[6], the concentrations in tissue and cells achieved will enable us to test the study hypotheses. Furthermore, longer dosing periods may yield less reliable data as participant adherence to study product use may vary over time.

2.2 Tenofovir 1% Gel

2.2.1 Description

Tenofovir 1% gel contains 1 gm/100 mL of PMPA (9-R-2-phosphonomethoxypropyl adenine monohydrate), an acyclic nucleotide analogue with activity *in vitro* against retroviruses, including HIV-1 and HIV-2, as well as hepadnaviruses.[7] Further information is available in the current version of the tenofovir gel Investigator's Brochure.

2.2.2 Mechanism of Action

Tenofovir is an acyclic nucleotide analogue of adenosine monophosphate. Tenofovir requires subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. At high concentrations, tenofovir diphosphate also inhibits HSV DNA polymerse and blocks viral replication. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.[7]

2.2.3 Strength of Study Product

The strength of the tenofovir gel is the strength (1%) previously tested in HPTN 050 (IND 55,690), CONRAD A04-095 (IND 73,382) and A04-099 (IND 73,382), HPTN 059 (IND 55,690), MTN-001 (IND 55,690), MTN-002 (IND 55,690), and CAPRISA 004. MTN-003 (IND 55,690), MTN-008 (IND 55,690) and CONRAD A10-113 (IND 73,382) are currently testing the same tenofovir 1% gel. The 4 mL application in this study delivers 40 mg of tenofovir.

2.3 *In vitro* Studies

2.3.1 *In vitro* Studies of Tenofovir

Anti-HIV-1 Activity

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes.[8] The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 µM - 8.5 µM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (NRTI) (abacavir [ABC], didanosine [ddI], lamivudine [3TC], stavudine [d4T], zalcitabine [ddC], and zidovudine [ZDV]), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine [DLV], efavirenz [EFV], and nevirapine [NVP]) and protease inhibitors (amprenavir [APV], indinavir [IDV], nelfinavir [NFV], ritonavir [RTV], and saquinavir [SQV]), additive synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values 0.5 µM - 2.2 µM) and showed strain-specific activity against HIV-2 (EC_{50} values ranged from 1.6 to 5.5 µM).

Resistance

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*.[8] These viruses expressed a K65R mutation in RT and showed a 2 – 4 fold reduction in susceptibility to tenofovir. Of note, this mutation also confers increased susceptibility to some other NRTIs, and is associated with approximately 50% reduction in the replicative capacity of HIV-1 (potentially resulting in a "less fit" virus).[9] Tenofovir-resistant isolates of HIV-1 have been recovered from some patients treated with Viread® in combination with certain antiretroviral (ARV) agents. In treatment-naïve patients, 8/47 (17%) isolates from patients failing Viread® + 3TC + EFV through week 144 showed >1.4 fold (median 3.7) reduced susceptibility *in vitro* to tenofovir. In treatment-experienced patients, 14/304 (5%) isolates from patients failing Viread® through week 96 showed >1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution. HIV-1 isolates from patients (n = 20) whose HIV-1 expressed a mean of 3 ZDV-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Multi-nucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

Cross-resistance

Cross-resistance among certain NRTIs has been recognized.[8] The M184V/I and/or K65R substitutions selected *in vitro* by the combination of FTC and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either 3TC or FTC, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

2.4 Animal Studies

Pharmacokinetics

Single-dose PK of vaginally-administered tenofovir gel in female rabbits has been previously examined (0.5 mL, 1% weight/volume (w/v) tenofovir, 5 mg/animal, 50 µCi/kg).[1] Plasma radioactivity concentrations were highest at the first sample time-point (0.5 hr) and below the level of quantitation at 24 hours. PK parameters including the proportion of dose absorbed systemically could not be estimated, due to very low plasma concentrations.

In a tissue distribution study using the same radio-labeled tenofovir (C-PMPA) 1% vaginal gel formulation, dose and strength as the above study, eighteen female rabbits were administered an intravaginal dose using a gavage needle.[10] An additional eighteen rabbits received an intravaginal dose of 3% w/v tenofovir (1.5 mg per animal). Analysis of vaginal tissue sections found no clear relationship between tissue concentration and dose, with no consistent pattern of distribution. Very little radioactivity was recovered in non-vaginal tissues. Concentrations in blood (0.002 to 0.047 µg-eq/g of tissue) exemplified the variability of distribution of the product although the effect of oral absorption due to grooming behaviors of the animals may have impacted these results.

The PK, excretion and tissue distribution of ^{14}C-PMPA were evaluated in rats following intravaginal administration of an earlier formulation of tenofovir gel containing propylene glycol.[10] Four female rats received a single intravaginal dose administered as an aqueous gel containing 20 mg tenofovir/g. Plasma concentrations of total radioactivity were highly variable; this was attributed to inconsistent retention of the formulation within the vagina, or possibly oral absorption related to grooming. The apparent maximum concentration (C_{max}) for tenofovir occurred at the earliest time-point (15 minutes), suggesting that absorption from the vagina was relatively rapid. Thereafter, plasma concentrations declined with an approximate half-life of 1.6 hours. The bioavailability of intravaginal tenofovir was estimated by comparison of the observed area under the curve $(AUC)_{(0\text{-}24)}$ with historical AUC data for an intravenous dose of 10 mg/kg tenofovir in rats (9.71 µg h/mL). The observed systemic bioavailability of intravaginal tenofovir was 7.9%.

In the excretion and distribution study, two groups of four additional rats received a single intravaginal dose of ^{14}C-PMPA (approximately 10 mg/kg, 100 µCi/kg) administered as aqueous gel containing 20 mg tenofovir/g. This study found that much of the dose was lost from the vaginal orifice by leakage. Vaginal tissue contained 0.1% of the dose and less than 0.01% of the dose was recovered in the ovaries and uterus.

The PK of C-PMPA was evaluated via plasma and vaginal biopsies collected from four rhesus monkeys following single-dose intravaginal tenofovir 1% vaginal gel.[10] Radioactivity was detected starting at 15 minutes post-application, with peak concentration of tenofovir in vaginal tissue at 8 hours and remaining high at 12 hours. No significant radioactivity was detected in whole blood or plasma.

Toxicology

The preclinical toxicity of tenofovir gel has been evaluated in 14-day rat and 10-day rabbit vaginal irritation and toxicity studies.[10,11] Daily intravaginal administration of tenofovir gel produced no vaginal irritation in rats (≤10% tenofovir) and minimal to mild vaginal irritation in rabbits (3% or 10% tenofovir).

14-Day Vaginal Irritation and Toxicity Study of Tenofovir Gel in Rats

Ten female Sprague Dawley rats/group received either 0% (vehicle control), 1%, 3%, or 10% tenofovir gel (2.5% HEC formulation) by intravaginal administration (0.5 mL/dose) once daily for 14 days. There were no mortalities, and no tenofovir-related clinical signs of toxicity or changes in body weight, food consumption, or absolute/relative kidney weights. Individual and mean vaginal (gross) irritation scores for all tenofovir-dosed animals sacrificed at Day 15 were graded as 0 (no erythema or edema); microscopic irritation scores for the vagina, cervix, ovaries, uterine horns, and vulva were graded as 0 (normal histology). No tenofovir-related histopathological effects on the vagina, cervix, ovaries, uterine horns, vulva, or kidneys were observed.

10-Day Vaginal Irritation Study of Tenofovir Gel in Rabbits

The potential irritant effects of tenofovir were evaluated in vaginal tissues of female New Zealand White rabbits using three different gel formulations (2.5% HEC or 1.0 – 2.0% Carbopol® 1342).[12] This study consisted of eleven treatment groups (five rabbits/group) that received either; a sham treatment or Conceptrol® (positive control); 0%, 0.3%, 1.0%, 3.0%, or 10.0% tenofovir formulated in the HEC placebo gel preparation; or 0% or 3.0% tenofovir formulated in a 1.0% or 2.0% Carbopol® 1342 gel preparation. With the exception of the sham dose group, all rabbits received dose formulation (1.0 mL/dose) daily applied topically to the mucosal surface of the vaginal vault for 10 consecutive days. No mortalities, tenofovir-related clinical signs of toxicity, or body weight changes were observed in this study. Group composite vaginal irritation scores for the 10% tenofovir topical gel (HEC formulation), 0% tenofovir (1.0% Carbopol® 1342 formulation), and Conceptrol® (positive control) dose groups were each rated as "mild." Composite vaginal irritation scores rated "minimal" were observed for all other tenofovir, vehicle or sham treatment groups, regardless of formulation. No unacceptable level of mucosal irritation was observed in any treatment group based on protocol-derived criteria for this animal model. Generalized erosion and/or ulceration were observed only in animals receiving Conceptrol® positive control (2 of 5) or 10% tenofovir gel (2 of 5).

2.4.1 Animal Studies of Tenofovir in Lactation

A pilot study evaluating the PK of tenofovir in breast milk was conducted by Van Rompay and colleagues in two healthy, lactating rhesus macaques.[13] Both macaques, whose infants were weaned prior to the PK study, had been lactating for more than 10 weeks. The macaques received a single subcutaneous dose of tenofovir (30 mg/kg) and blood samples were collected pre-dosing as well as 0.5, 1, 2, 4, 8, and 24 hours post-dosing. Tenofovir was detected in the milk of both animals. However, the peak concentrations (0.808 µg/mL and 0.610 µg/mL) were very low at approximately 2 to 4% of the concentrations detected in serum (18.3 µg/mL and 30.2 µg/mL). These data

suggest that lactating women using tenofovir vaginal gel should have undetectable or very low levels of tenofovir in their breast milk, and thus maternal gel use will likely be of no clinical significance to nursing infants. Additional studies of tenofovir conducted in rhesus macaques further demonstrate the safety of prolonged administration of tenofovir in newborn and infant macaques.[14,15]

2.5 Clinical Studies

2.5.1 Clinical Studies of Tenofovir

Pharmacokinetics

A Phase 1 Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel, also known as HPTN 050, a study of tenofovir vaginal gel with published data, examined the PK of tenofovir gel.[16] Eighty-four (60 HIV negative and 24 HIV positive) women applied either 0.3% or tenofovir 1% gel once or twice daily for 14 days. Systemic absorption was limited (maximum serum levels 3.1-25.8 ng/mL).

A randomized trial to assess anti-HIV activity and soluble mucosal immunity following application of tenofovir gel also provided data on the PK of tenofovir gel.[17] With daily dosing, 12 participants in the tenofovir arm of the study yielded mean (SD) CVL tenofovir levels at Days 3, 7, and 14 of 9.5×10^3 (11.2×10^3), 24.7×10^3 (26.4×10^3), and 16.0×10^3 (20.5×10^3) ng/mL, respectively.

A study of the pharmacokinetics of tenofovir gel was conducted among 49 sexually abstinent women in the USA and Dominican Republic (CONRAD A04-095, IND 73,382).[18] The following are results from a subset (n=21) who completed the single-dose phase. Following an intravaginal dose (4 g) of tenofovir gel, blood samples were obtained at 0.5, 1, 2, 4, 6, 8, and 24 hr(s) from all participants. Participants were randomized to one of seven time-points [0.5, 1, 2, 4, 6, 8, and 24 hr(s)] for vaginal fluid collection and vaginal biopsies. Total tenofovir (TFV) was measured in blood plasma, fluid, and biopsies. Most blood plasma TFV concentrations were below 5 ng/mL. Four had higher values (up to 19.5 ng/mL), which were not sustained. Vaginal fluid concentrations were high, generally $1.5\text{-}5.0 \times 10^6$ ng/mL through 8 hrs and $4.5\text{-}47.1 \times 10^4$ ng/mL at 24 hrs. The mean concentration in vaginal tissue at 0.5, 1, 2, 4, 6, 8 and 24 hr(s) were 275×10^3, 450×10^3, 186×10^3, 89×10^3, 69×10^3, 24×10^3 and 15×10^3 ng/g of tissue, respectively, (LLOQ=1 ng/mL) with a peak at 1-4 hrs. Vaginal fluid elimination appeared linear. Tissue elimination appeared to follow a multi-compartment model. Total TFV was detectable in vaginal tissue and fluid up to 24 hrs post single-dose exposure.

MTN-001 was a Phase 2 study of adherence to and pharmacokinetics of oral and vaginal preparations of tenofovir among 144 sexually active HIV-negative women at sites in Uganda, South Africa and the United States, who at the end of the 21-week study followed each regimen (oral, vaginal and a combination of oral and vaginal) for six weeks. MTN-001 results were presented at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) in late February 2011. All three study regimens (TDF

300 mg tablet, tenofovir 1% gel and a combination of the TDF 300 mg tablet and tenofovir 1% gel) were well tolerated and found to be acceptable. A statistically significant preference for oral product was noted (p=0.002) and this was largely driven by US sites. Self-reported adherence across sites was high (94%). Vaginal tissue drug levels were 2 $\log_{10}$ higher after vaginal dosing compared to oral dosing.[17]

Safety

In HPTN 050, the tenofovir 1% gel formulation was well-tolerated in both HIV-uninfected and -infected women.[19] Ninety-two percent reported at least one AE. The majority of these events were mild (87%) and limited to the genitourinary tract (77%). The five most frequently reported mild genital AEs were pruritus (n = 18), erythema (n = 14), petechiae/ecchymosis (n = 14), vaginal discharge (n = 13), and burning (n = 10). Four severe AEs were reported, but only one (lower abdominal pain) was thought to be product-related. Product concentration, sexual activity and HIV status were not associated with a specific AE pattern. No clinically significant systemic toxicity was observed. No serious adverse events (SAEs) were reported.

Among 84 female participants in HPTN 050, 76 had bacterial vaginosis (BV) evaluation (using Nugent score criteria) at both enrollment and Day 14. Of these, 30 women had asymptomatic BV at baseline; 15 of these were found to be BV negative on Day 14. Among 46 women without BV at baseline, one had BV detected at 14 days. Overall, 40% of the women had asymptomatic BV at baseline compared to 21% of the women after fourteen days of tenofovir gel use (p = 0.0005), suggesting that the gel did not increase women's risk of developing BV.[19]

In a male tolerance study (CONRAD A04-099/IND 73,382), tenofovir 1% gel was well-tolerated in men following seven days of once-daily penile exposure.[20] There were few genital findings observed after product use and all findings were classified as mild, small in size and requiring no treatment. Reported symptoms were mild, of short duration and resolved by the final visit. There were no noticeable differences between signs and symptoms of genital irritation in the circumcised compared to uncircumcised group. Tenofovir gel applied to the penis for seven days was well-tolerated locally and systemically, and it is unlikely that male partners exposed to small amounts of tenofovir gel will experience significant genital or systemic toxicity.

A Phase 2 study of tenofovir 1% gel (HPTN 059) assessed safety and acceptability of, and adherence to, a regimen of tenofovir gel for vaginal use in HIV-uninfected women versus a placebo gel. Exploratory objectives included measurement of vaginal flora characteristics, assessment of the effects of gel on genital cytokine and chemokine expression, and the evaluation of cytokine and chemokine expression to correlate expression with evidence of inflammation, epithelial disruption and genital symptoms. The study was a four-arm, three-site, randomized, controlled trial comparing gel used once daily and gel used prior to intercourse, to placebo gel, with 6 months gel exposure and follow-up. The study was conducted among 200 women in Pune, India; Birmingham, Alabama, USA; and New York, New York, USA. Participants were sexually active, HIV-uninfected women aged 18 to 50, but not menopausal or post-

menopausal. Participants received single-use unit dose tubes and single-use applicators.

No statistically significant differences were seen between those receiving active and placebo gels in complete blood count (CBC), liver function tests, or renal function tests. Among women using study gel, no participants had pelvic exam findings involving generalized erythema or severe edema or deep epithelial disruption at any follow-up visit during the study. At the Week 24 Visit, no participants had exam findings suggestive of vaginitis, cervicitis, superficial disruption, disrupted blood vessels, or intermenstrual bleeding. Adherence to study gel was high, and was supported by PK data. 79% of women reporting gel use in past 12 hours had low but detectable plasma tenofovir supporting self-reported adherence data. Daily and coital use was highly acceptable to women. These data suggest a favorable safety and acceptability profile of tenofovir gel.[21]

In MTN-002, the first microbicide trial to be conducted during pregnancy, 16 women received a single vaginal dose of tenofovir 1% gel prior to elective cesarean section. Blood, amniotic fluid, cord blood, endometrial tissue, and placental tissue were collected from participants.[22] Plasma tenofovir levels were compared to historical controls. Study results demonstrated that tenofovir levels following a single vaginal dose of tenofovir 1% gel in pregnant women were similar to those found in non-pregnant women, and that levels were up to 50 – 100 times less compared to standard oral dosing. Tenofovir was detectable in the fetal compartment, with low overall cord levels (approximately 40 times less than observed in oral dosing), but with a similar cord blood: maternal ratio. Overall, findings suggest that tenofovir is safe for use in term pregnancy and warrants additional investigation of repeat dosing during pregnancy.

RMP-02/MTN-006 was a Phase 1 study designed to evaluate the safety and early pharmacokinetic profile of 1% vaginally-formulated tenofovir gel, applied rectally, during a single exposure followed by once-daily dosing for 7 days, as compared to a single oral dose. Rectal dosing with the vaginal formulation of tenofovir 1% gel was found to be neither entirely safe nor fully acceptable. A regimen of 7 rectally applied daily doses of tenofovir 1% gel resulted in significant inhibition of ex vivo HIV challenge of biopsy tissue, whereas neither single dosing of oral (TDF) nor single rectal (TFV) dosing resulted in significant protection of tissue against ex vivo viral challenge.[23]

Effectiveness for Prevention of HIV

The CAPRISA 004 trial was a Phase 2B trial designed to assess the effectiveness and safety of a tenofovir 1% vaginal gel, for the prevention of HIV acquisition in women.[16] A double-blind, randomized, controlled trial was conducted comparing tenofovir gel (n = 445) with placebo gel (n = 444) when used in a pericoital regimen, in sexually active, HIV-uninfected 18 to 40 year-old women in urban and rural KwaZulu-Natal, South Africa. HIV serostatus, safety, sexual behavior and gel and condom use were assessed at monthly follow-up visits for 30 months. HIV incidence in the tenofovir gel arm was 5.6 per 100 women-years, compared to 9.1 per 100 women-years in the placebo gel arm (incidence rate ratio = 0.61; P = 0.017). Tenofovir gel reduced HIV acquisition by an

estimated 39% overall, and by 54% in women with high gel adherence. No increase in the overall adverse event rates was observed.

Resistance
In HPTN 050, no new resistance mutations evolved in plasma or cervicovaginal lavage after 14 days of tenofovir gel use, but 3 women had plasma mutations associated with low-level tenofovir resistance identified at both Days 0 and 14 (M41L, L210M, ±T215I/Y). In CAPRISA 004, there were no differences in viral load among seroconverters on tenofovir compared to placebo and no tenofovir-resistant mutations were observed in HIV seroconverters, using standard tests for detection of drug resistant strains of HIV.

2.6 Study Hypothesis and Rationale for Study Design

2.6.1 Study Hypothesis

- Coitus will not impact the pharmacokinetics of TFV following a single precoital dose, BAT or multiple applications of study product

- Coitus will not alter the antiviral activity in genital tract secretions following single precoital dose, BAT or multiple applications of study product

2.6.2 Rationale for Study Design

This study will assess the impact of barrier unprotected vaginal intercourse on the PK and PD of tenofovir 1% gel following different vaginal dosing regimens related to the time of sex: single precoital dose at 1 hour, 24 hours or a single dose 1 hour before and 1 hour after (BAT) (Group 1) or 7 daily applications with the 7^{th} dose administered at -1 hour or -72 hours (Group 2). Pharmacological and mucosal immunity assessments will be made under four test conditions: no gel/no coitus (baseline), no gel/coitus (Group 1 only), gel/no coitus, and gel/coitus. Specific pairwise comparisons will be made between test conditions to assess the effects of sex and the effects of gel on PK, PD, and mucosal immunity variables.

Pharmacokinetics
The current study will build from the prior PK studies and assess drug dilution and displacement in the vaginal lumen (CVL and cytobrush), rectal lumen (rectal sponge) and vaginal and cervical tissue (vaginal and cervical biopsies) in the absence of, or following, coitus. A semen biomarker measured in CVL will be used to estimate the volume of ejaculate and its contribution to drug dilution.

Pharmacodynamics
The anti-HIV-1 and anti-HSV-2 activity in CVL will be measured as a surrogate of tissue PD. This antiviral activity will reflect both the biological activity of luminal drug as well as the endogenous antimicrobial activity of female genital tract secretions. Prior studies indicate that the activity correlates with CVL drug levels.[17] While the PD of tenofovir gel might best be measured by challenging vaginal or cervical tissue *ex vivo*, the variability

in susceptibility of tissue to HIV renders this a difficult strategy and therefore we have prioritized the measurements of drug levels (PK) in biopsy samples.[5]

2.6.3 Justification of Dosing

Choice of the tenofovir 1% gel concentration for MTN-011 is based on both animal and clinical evidence suggesting an appropriate safety profile and potency and efficacy in CAPRISA 004. Animal and human studies have demonstrated minimal vaginal irritation at this concentration. A rabbit vaginal irritation test identified tenofovir 1% gel as being histopathologically identical to sham or control treatment, while on a qualitative basis 3% gel was more irritating to vaginal epithelia. The tolerability of the 1% gel was confirmed in the HPTN 050 Phase 1 study and the HPTN 059 expanded safety study, as well as the CONRAD tissue PK and male tolerance studies. Effectiveness data from CAPRISA 004 showed that tenofovir 1% gel reduced HIV acquisition by an estimated 39% overall (p=0.017).[1] The 1% gel concentration is currently being evaluated in MTN-003 (IND 55,690), MTN-008 (IND 55,690), CONRAD A10-113 (IND 73,382) and, via registry in MTN-016.

Given the safety and efficacy data-to-date, establishing the impact of coitus and semen on the tenofovir 1% gel formulation when delivered vaginally either daily or in a coitally-dependent fashion will complement available trial results from CAPRISA 004 and MTN-003.

2.7 Additional Protocol Considerations

Rationale for Enrolling Mutually Monogamous Couples

As part of the study procedures, participants will be asked to have sex without condoms. Because a correlation between sexually transmitted infections and non-monogamy is known to exist,[24] the protocol enrolls couples who have been in mutually monogamous sexual relationships for the past 6 months and who intend to stay in these committed relationships for the next 4 months; additionally these couples need to be currently engaging in sex without condoms as part of their normal coital routine. Thus, couples enrolled into MTN-011 will be at no increased risk of sexually transmitted infections as a result of study participation because they will experience no change to their current sexual behavior. Participating couples will be counseled regarding HIV and STI risk reduction, including the importance of monogamy and will be screened for STIs and HIV.

3 OBJECTIVES

3.1 Primary Objectives

1. To assess the impact of coitus (and semen) on the pharmacokinetics of tenofovir 1% gel in female genital tract secretions, vaginal and cervical tissue and rectal tract secretions

2. To assess the impact of coitus (and semen) on pharmacodynamics of luminal drug by measuring the anti-HIV-1 activity in CVL samples

3.2 Secondary Objective

1. To assess the acceptability of the MTN-011 trial to male and female participants

3.3 Exploratory Objective

1. To determine impact of coitus and/or tenofovir on the genital tract mucosal environment
2. To determine whether a semen biomarker can be used to estimate the volume of ejaculate within CVL
3. To assess whether sufficient drug is retained in the lumen in the absence of or following coitus to inhibit HSV-2 as an additional surrogate biomarker of pharmacodynamics

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-011 is a Phase 1, multi-site, non-randomized, multi-sequence, open-label study evaluating the impact of coitus on PK and PD of tenofovir 1% gel following a single dose and BAT regimen or a multiple dosing regimen.

4.2 Summary of Major Endpoints

Pharmacokinetics

1. Tenofovir and tenofovir diphosphate levels
   - Cervicovaginal lavage
   - Cervical cytobrush
   - Tissue biopsies (vaginal and cervical)
   - Blood
   - Rectal sponge

Pharmacodynamics

2. Anti-HIV-1 activity in CVL

4.3 Description of Study Population

The study population consists of sexually active heterosexual monogamous couples who meet the eligibility criteria outlined in Section 5.

4.4 Time to Complete Accrual

The approximate time to complete study accrual and follow-up is expected to be 6-12 months.

4.5 Study Groups

Two study cohorts are planned:

1.) Group 1: Single Dose/BAT Cohort
2.) Group 2: Multiple Dose Cohort

4.6 Expected Timing of Trial Visits

Acknowledging that it is not always possible to complete study evaluations/visits on the targeted dates/times, evaluations/visits may be completed within a specified window (see MTN-011 Study Specific Protocol (SSP) Manual) around the target date/time.

4.7 Expected Duration of Participation

The expected duration for Group 1 participants is approximately 8 weeks from the date of enrollment and approximately 14 weeks from date of enrollment for Group 2. The expected duration of participation does not include the 30-day screening period.

4.8 Sites

Sites selected by the MTN Executive Committee will participate in MTN-011.

5 STUDY POPULATION

5.1 Selection of the Study Population

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

5.1.1 Recruitment

Heterosexual couples will be recruited from a variety of sources. The study will recruit couples, but since the female is required to undergo more visits and procedures while on study than the male partner, women-focused venues of recruitment may be emphasized, such as family planning and gynecology clinics, as well as local HIV/AIDS and social service organizations, colleges and universities, and community-based locations. Sites will also actively recruit couples by distributing flyers and other printed materials throughout the community that target heterosexual couples, contacting prior HIV microbicide trial participants (women) or other individuals who have expressed interest in clinical trials and who have agreed to be contacted, running advertisements in local publications, and conducting education and outreach activities at local community agencies and other venues**.**

Participants will also be referred to the study from other local research projects and other health and social service providers serving the target study population. All recruitment materials will be approved by site Institutional Review Boards (IRBs) prior to use. Site community representatives will advise on these materials before they are submitted to the IRB for review.

5.1.2 Retention

Once a participant is enrolled in MTN-011, the study site will make every effort to retain the participants in follow-up to minimize possible bias associated with loss-to-follow-up. Enrollment is defined as the completion and final sign-off of the eligibility checklist. Each study site will establish and follow standard operating procedures (SOPs) for participant retention. A retention rate of 100% will be targeted.

5.1.3 Other Screening Considerations

Previous participation in Group 1 or Group 2 of the MTN-011 clinical trial is not exclusionary.

Repeat testing to confirm study eligibility is not required for Group 1 or Group 2 participants who have successfully completed their study participation and wish to continue study involvement by enrolling in the opposite group, provided that no more than 90 days have passed since the participants' last study visit (see MTN-011 SSP

Manual for additional details). A 30 day minimum washout period is required prior to enrollment into the opposite group.

5.2 Inclusion Criteria

Men and women in Group 1 and Group 2 must meet the following criteria to be eligible for inclusion in the study:

1. Able and willing to provide the following:

    a. Written informed consent to be screened for and take part in the study

    b. Adequate locator information, as defined in site SOPs

2. Per participant report, at low risk for HIV/STI. Low risk is defined as:

    a. No STIs in the 6 months prior to Screening

    b. No non-therapeutic intravenous drug use in the 18 months prior to Screening

    c. In a mutually monogamous relationship with a partner of the opposite sex for 6 months prior to Screening and the intent to stay in this relationship for the next 4 months

3. At Screening and Enrollment, both partners independently report not using barrier contraception and/or barrier protection as part of normal coital routine and report the intent to continue said sexual practice for the duration of study participation

4. HIV-uninfected based upon testing performed by study staff at Screening (per protocol algorithm)

5. Agrees not to participate in other research studies involving drugs, medical devices, or genital and rectal products, or large blood draw studies during study participation

6. <u>Women</u> must also meet the following criteria:

    a. Age 21 through 46 years (inclusive) at Screening, verified per site SOPs

    b. Pap result in the 12 calendar months prior to Screening consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), or satisfactory evaluation with no treatment required

of non-Grade 0 Pap result per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines in the 12 calendar months prior to the Screening Visit

Note: Women with a documented normal result within the 12 months prior to screening need not have a Pap smear during the screening period. Women with abnormal Pap smears can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology). Need for a repeat Pap within 6 months does not preclude enrollment prior to that result becoming available.

c. Must be currently using effective non-barrier contraception, other than a contraceptive vaginal ring or intrauterine device, for at least three months prior to Screening (i.e., oral contraceptive, patch, injectable hormones, subdermal implants, female or male sterilization) and intending to use this method for the course of the study

d. Per participant report, regular menstrual cycles with at least 21 days between menses (does not apply to participants who report using a progestin-only method of contraception at screening, e.g., Depo-Provera)

Note: This criterion is not applicable to participants using continuous combination oral contraceptive pills, as the absence of regular menstrual cycles is an expected, normal consequence in this context.

e. Anatomy sufficient for performing pelvic examinations and for collecting vaginal and cervical specimens

f. Female participants must also agree to abstain from intercourse (oral, anal, or penile-vaginal) and other vaginal practices (e.g., masturbation, douching, tampon use, application of lubricants/spermicides or other related practices) 72 hours prior to each follow-up visit. Group 2 participants must agree to also abstain from the aforementioned practices throughout the at-home gel use period

7. <u>Men</u> must also meet the following criteria:

a. Age 21 or older at Screening, verified per site SOPs

b. Agree to abstain from intercourse (oral, anal, or penile-vaginal) and other penile practices (e.g., masturbation, application of lubricants/spermicides or other related practices) 72 hours prior to each follow-up visit. Group 2 participants must also agree to refrain from intercourse (oral, anal, or penile-vaginal) throughout their partner's at-home gel use period

5.3 Exclusion Criteria

Men and women who meet any of the following criteria will be excluded from the study. Previous participation in Group 1 or Group 2 of the MTN-011 clinical trial is not exclusionary.

1. Participant report of any of the following:

    a. Known allergy to the study product (ever)

    b. Post-exposure prophylaxis (PEP) for HIV exposure within 6 months prior to Screening

    c. Participation in any other research study involving drugs, medical devices, or genital products 30 days or less prior to Enrollment

    d. Plans to relocate away from the study site in the next 4 months

    e. History of domestic violence with current partner (ever)

    f. Systemic or topical antimicrobials within the last 7 days prior to Enrollment

    g. Currently using or planning to use pharmacologic immune modulator(s)

2. At Screening or Enrollment, symptomatic urinary tract infection (UTI)

    Note: Otherwise eligible participants diagnosed with UTI during screening are offered treatment and may be enrolled after completing treatment and all symptoms have resolved as long as treatment is completed and all symptoms have resolved within 30 days of obtaining informed consent for Screening/Enrollment.

3. At Screening, has a positive hepatitis B surface antigen (HBsAg) test result

4. At Screening or Enrollment, has an STI or reproductive tract infection (RTI) requiring treatment per current CDC guidelines

5. Genital signs and/or symptoms of Grade 2 or higher

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

    Note: Otherwise eligible participants with exclusionary genital findings may be enrolled after the findings have improved to a non-exclusionary severity grading or resolved as long as treatment is completed and all symptoms have resolved within 30 days of obtaining informed consent for Screening/Enrollment.

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

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

    a. Participant report (or clinical finding) of the following:

        i. Last pregnancy outcome 90 days or less prior to Enrollment

        ii. Currently pregnant

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

        iii. Currently breastfeeding

        iv. Intends to become pregnant in the next 4 months

        v. Gynecologic or genital procedure (e.g., tubal ligation, dilation and curettage) within the prior 30 days to Enrollment

            Note: This does not include biopsy for the evaluation of an abnormal pap result or endometrial biopsy that occurred more than 7 days prior to Enrollment.

    b. Any of the following laboratory abnormalities at Screening:

        i. Hemoglobin less than 10.0 g/dl

        ii. Platelet count less than 100,000/mm^3

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

    c. Use of a vaginal douche or other intravaginal products (excluding tampon use) in the 30 days prior to Enrollment

    d. Currently menopausal or perimenopausal

8. Men who meet any of the following criteria will be excluded from the study:

    a. Participant report of penile procedures (e.g. biopsy, circumcision) within 42 days prior to Enrollment

    b. For uncircumcised men, per participant report, treatment of candidal balanoposthitis/ balanitis within 30 days prior to Enrollment

5.4 Co-enrollment Guidelines

As indicated in Section 5.2, participants should not take part in other research studies involving drugs, medical devices, or genital/rectal products after the Screening Visit and while taking part in MTN-011. Participation in the following types of studies may be allowed at the discretion of the IoR/designee:

- Participants may take part in ancillary studies approved by MTN-011 Protocol Chair
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-positive persons
- Participants who become pregnant may take part in observational pregnancy studies, including registries, approved by the MTN-011 Protocol Chair

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-011, the IoR/designee will consult the PSRT regarding potential safety considerations associated with co-enrollment.

6 STUDY PRODUCT

6.1 Regimen

This study involves two cohorts, a Single Dose/BAT Cohort (Group 1) and a Multiple Dose Cohort (Group 2). Both cohorts will insert tenofovir 1% gel.

6.2 Administration

Study staff will provide participants with study product use instructions into both Group 1 and Group 2 on how to properly administer the study product. Panty liners will be offered to female participants in an effort address any leakage issues. If a participant in Group 2 misses a dose during the home administration phase they will be instructed to administer the missed dose as soon as possible. If the next dose is due within 6 hours, the missed dose will be skipped and the next dose will be administered as originally scheduled. This 6-hour time limit provides a window of time for participants to safely make up a missed dose while avoiding administration of overlapping doses.

When product use is associated with the act of coitus, if coitus does not occur, the visit will be rescheduled after a sufficient washout period and additional study product will be dispensed.

6.2.1 Group 1 (Single Dose/BAT Cohort Group)

Table 3: Group 1 Gel Schedule

Gel	Visit	Visit Name	Number of doses dispensed	Location of use	Timing of gel use relative to coitus
-1 hr	3a	Gel -1/Coitus	1	Hotel or comparable location	-1 hr
	3b	Post-Coital Sampling			
	4a	Gel -1/No Coitus	1	Clinic	
	4b	Sampling*			
-24 hr	5a	Gel -24/Coitus	1	Clinic	-24 hr
	5b	Post-Coital Sampling			
	6a	Gel -24/No Coitus	1	Clinic	
	6b	Sampling*			
BAT	7a	Gel -1/Coitus/ Gel +1	2	Hotel or comparable location	1 hr before coitus And 1 hr after coitus
	7b/ Final	Post-Coital Sampling			

**The collection of samples should be matched to the collection of samples of the preceding gel/coitus visit timing.*

At Visit 3a (Gel -1hr/Coitus), females in this single dose gel group, will insert into the vagina the content of one applicator of tenofovir 1% gel approximately 1 hour prior to engaging in coitus; the study product will be vaginally inserted at the location where coitus is to occur (hotel or comparable site). Following a minimum 10-day washout period, to allow for clearance of any residual drug, the female participant will return to the clinic for Visit 4a (Gel/No Coitus), and will apply a vaginal dose of one applicator of tenofovir 1% gel in the clinic.

After a minimum 10-day washout period, couples will return to the clinic for Visit 5a/b (Gel -24hr/Coitus), females will insert into the vagina the content of one applicator of tenofovir 1% gel at the clinic approximately 24 hours prior to engaging in coitus. At Visit 5a; the study product will be inserted at the clinic. Following a minimum 10-day washout period, the female participant will return to the clinic for Visit 6a (Gel -24/No Coitus) and will apply one applicator of tenofovir 1% gel in the clinic and will be required to return approximately 24 hours later for Visit 6b (Sampling).

Following a minimum 10-day washout period, couples will return for Visit 7a (Gel -1 hr/Coitus/ Gel +1 hr), females will insert into the vagina the content of one applicator of tenofovir 1% gel approximately 1 hour prior to engaging in coitus and a second dose will be inserted approximately 1 hour after coitus. Both doses of the study product will be vaginally inserted at the location where coitus is to occur (hotel or comparable site).

6.2.2 Group 2 (Multiple Dose Cohort)

Table 4: Group 2 Gel Schedule

Gel	Visit	Visit Name	Number of doses dispensed	Location of use	Timing of final dose of gel relative to coitus
	1	Screening (Baseline CVL)			
	2	Enrollment- Provision of Study Product	7**	1 Clinic 5 Home	
-1 hr	3a	Gel -1/Coitus	1	1 Hotel or comparable location	-1 hr
	3b	Post-Coital Sampling			
	4	Provision of Study Product	7**	1 Clinic 5 Home	
	5	Sampling*	1	1 Clinic	
-72 hr	6	Provision of Study Product	8**	1 Clinic 6 Home	
	7a	Gel -72/Coitus			-72 hr
	7b	Post-Coital Sampling			
	8	Provision of Study Product	8**	1 Clinic 6 Home	
	9/ Final	Sampling*			

*The collection of samples should be matched to the collection of samples of the preceding gel/coitus visit timing.
**Participants will be given one extra dose, see Section 6.5 for additional details.

At Visit 2 (Enrollment/ Provision of Study Product) while in the clinic, the female participant will vaginally administer the content of one applicator of tenofovir 1% gel. For the next five consecutive days she will vaginally insert the content of one applicator of tenofovir 1% gel daily at home (i.e., doses 2-6). Doses should be inserted at approximately the same time each day. At Visit 3a (Gel -1hr/Coitus) the couple will return to the clinic to review procedures and the female participant will insert into the vagina the content of one applicator of tenofovir 1% gel (i.e., the 7^{th} dose) at the location where coitus is to occur (hotel or comparable site). This dose should be applied approximately 1 hour prior to coitus. Following a minimum washout period of 20 days to allow for clearance of any residual drug and to provide time for the participant's menstrual period, the female participant will return to the clinic for Visit 4 (Provision of Product) and insert into the vagina the content of one applicator of tenofovir 1% gel. For the next five consecutive days she will insert into the vagina the content of one applicator of tenofovir 1% gel daily at home (i.e., doses 2-6). Doses should be inserted at approximately the same time each day. At Visit 5 (Sampling) the participant will return to the clinic and insert into the vagina the content of one applicator of tenofovir 1% gel (i.e., 7^{th} dose).

At Visit 6 (Provision of Product) while in the clinic, the female participant will vaginally administer the content of one applicator of tenofovir 1% gel. For the next six consecutive days she will vaginally insert the content of one applicator of tenofovir 1% gel daily at home (i.e., doses 2-7). Doses should be inserted at approximately the same time each day. Approximately 72 hours after the administration of the last vaginal dose, couples will return to the clinic for Visit 7a (Gel -72/Coitus). Following a minimum washout period of 20 days to allow for clearance of any residual drug and to provide time for the participant's menstrual period, the female participant will return to the clinic for Visit 8 (Provision of Product) and insert into the vagina the content of one applicator of tenofovir 1% gel. For the next six consecutive days she will insert into the vagina the content of one applicator of tenofovir 1% gel daily at home (i.e., doses 2-7). Doses should be inserted at approximately the same time each day. The final dose of gel should be administered approximately 72 hours prior to Visit 9/Final (Sampling).

6.3 Study Product Formulation

The tenofovir 1% gel is a gel formulation of tenofovir (PMPA, 9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate), formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, HEC, and pH adjusted to 4-5. Tenofovir 1% gel is a transparent, viscous gel that will be supplied in pre-filled, single-use applicators. Each pre-filled applicator will contain a dose of approximately 4 mL of tenofovir gel, equal to 4.4 g of gel.

The tenofovir 1% gel should be stored at 25°C (77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F).

6.4 Supply and Accountability

6.4.1 Study Product Supply

The tenofovir 1% gel will be supplied by CONRAD (Arlington, VA, USA).

6.4.2 Accountability

Each site PoR is required to maintain complete records of all study product received and dispensed. All unused study products must be returned to MTN CORE Pharmacist after the study is complete unless otherwise instructed by the MTN CORE Pharmacist. Procedures to be followed will be provided in the MTN-011 Pharmacy Instruction Manual.

6.5 Study Product Dispensing

Study products are dispensed by the site pharmacy to the study staff on behalf of enrolled participants, 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 FDA 1572 Form.

For both Group 1 and 2, the doses that will be administered in the clinic will be dispensed on the day of the clinic visit. The dose in Group 1 and Group 2 that is to be self-administered at the hotel (or comparable site) just prior to coitus will be dispensed on that day at the clinic. Group 2 participants will receive 6 pre-filled applicators of tenofovir 1% gel at the clinic visit just prior to each of the at home administration periods at Visit 2 and Visit 4. This will provide applicators for doses 2-6 and one extra should an applicator become unusable for any reason. Group 2 participants will receive 7 pre-filled applicators of tenofovir 1% gel at the clinic visit just prior to each of the at home administration periods at Visit 6 and Visit 8. This will provide participants with applicators for doses 2-7. This will provide one extra dose should an applicator become unusable for any reason.

6.6 Retrieval of Unused Study Products

It is anticipated that for participants in Group 2 unused applicator will be returned to the study site following each consecutive administration at home, unless a replacement applicator is needed by the participant. Study participants in Group 2 will be instructed to return all unused applicators to the site. Unused applicators will be counted and documented, then sent to the pharmacy and placed in quarantine. . The PoR will document all product returns and store returned study products in designated areas within the study pharmacy.

See Section 6.7 for information on the retrieval of used applicators.

6.7 Study Product Counseling and Adherence

Study Product Adherence Counseling

Participants in Group 2 will receive study product adherence counseling at visits where gel is dispensed, if necessary. Site staff will counsel female participants to insert a full applicator of gel daily at approximately the same time each day. Female participants in both groups will be counseled to abstain from intercourse (oral, anal, or penile-vaginal) and other vaginal practices (e.g., masturbation, douching, tampon use, application of lubricants/spermicides or other related practices) 72 hours prior to each follow-up visit. Group 2 female participants will also be counseled to abstain from the aforementioned practices during the at-home gel use periods.

Men will be counseled to abstain from intercourse (oral, anal, or penile-vaginal) and other penile practices (e.g., masturbation, application of lubricants/spermicides or other

related practices) 72 hours prior to each follow-up visit. Group 2 male participants will also be counseled to refrain from engaging in intercourse (oral, anal, or penile-vaginal) during their partner's at-home gel use periods.

Adherence

Reminder Phone Calls
Female participants in Group 2 will receive reminder phone calls or short message service (SMS) as a method of adherence enhancement.

Product Adherence Assessments
Female participants' behaviors in Group 2 regarding study gel use will be collected via standardized questions developed by the protocol team in conjunction with study site staff and community representatives, to maximize the accuracy of self-reported data.

Retrieval of Used Applicators
Female participants in Group 1 will return their used applicator following coitus.

Female participants in Group 2 will be instructed to return all used applicators to the clinic at each visit following the at-home doses. The used applicators will be collected in the clinic and documented.

See Section 6.6 for instruction on the retrieval of unused applicators.

6.8 Concomitant Medications

With the exception of medications listed as prohibited, enrolled study participants may use concomitant medications during study participation. All concomitant medications, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs, and herbal preparations reported throughout the course of the study will be recorded on case report forms designated for that purpose.

6.9 Prohibited Medications and Practices

Concomitant use of prohibited non-study products (e.g., female use of lubricants) and other practices, including but not limited to intercourse (oral, anal, or penile-vaginal), masturbation, or other related practices 72 hours prior to each follow-up will be assessed. In addition, Group 2 female participants will be asked to refrain from these practices while dosing with gel at home and Group 2 male participants will be asked to refrain from engaging in intercourse during the at-home gel use period.

Participants will be counseled to avoid such use of the aforementioned products/practices when appropriate.

The use of immune modulators is prohibited. Participants requiring the use of these agents should not be included in the trial.

Participants are not expected to require gynecologic surgical procedures during follow-up; however, should such a procedure be required, the IoR/designee will consult the PSRT regarding ongoing product use by the participant.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is presented in Appendices I and II. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites are provided in the MTN-011 SSP Manual available at www.mtnstopshiv.org/.

7.1 Pre-screening

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

7.2 Group 1 (Single Dose/BAT Cohort)- Screening Visit (Visit 1)

A Screening Visit (Visit 1) may take place up to 30 days prior to the Enrollment Visit (Visit 2a No Gel/Coitus). Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed consent for screening will be obtained before any screening procedures are initiated. Both the female and the male must meet the eligibility requirements for the couple to be eligible. For participants who do not meet the eligibility criteria (e.g., STI or HIV-positive, self-reported non-monogamy, etc.), screening will be discontinued for the couple once ineligibility is determined.

All test results will be provided to an individual participant in a private room to ensure participant confidentiality. If a participant is found to be ineligible based upon STI or HIV status, study staff will not inform the infected participant's partner. Participants may choose to disclose this information on their own. Study staff will comply with local requirements to report communicable diseases including HIV-1 identified among study participants to health authorities.

In addition, if one partner admits to non-monogamy, study staff will inform the couple that they are ineligible for the study; however non-monogamy will not be disclosed to the couple as the reason for ineligibility.

All individuals who come to the clinic for screening will be provided counseling regarding HIV/STI prevention see Table 6. Participants will be informed that condoms are the only known way to prevent HIV and other STIs.

Note: Participants may rescreen a total of one time; however both the female and male must meet the eligibility requirements at the time of the rescreening.

Table 5: Group 1 Study Visit Schedule

Group 1- Single Dose/BAT Cohort				
Gel	**Visit**	**Visit Name**	**Targeted Visit Schedule**	**Coitus**
	1 ♂♀	Screening		
	2a ♂♀	Enrollment/ No Gel/ Coitus	To occur ~2-3 days after the final day of the female's last period*	X
	2b♀	Post-Coital Sampling	To occur ~2 hrs after coitus	
-1 hr	3a ♂♀	Gel -1/Coitus	To occur ~3-7 days after Visit 2	X
	3b♀	Post-Coital Sampling	To occur ~2 hrs after coitus	
	4a ♀	Gel -1/No Coitus	To occur after a min.10-day washout period	
	4b ♀	Sampling	See Visit 3b for details	
-24 hr	5a ♂♀	Gel -24/Coitus	To occur after a min.10-day washout period	X
	5b ♀	Post-Coital Sampling	To occur ~2 hrs after coitus	
	6a ♀	Gel -24/No Coitus	To occur after a min.10-day washout period	
	6b ♀	Sampling	See Visit 5b for details	
BAT	7a ♂♀	Gel -1/Coitus/ Gel +1	To occur after a min.10-day washout period	X
	7b/ Final ♂♀	Post-Coital Sampling	To occur ~2 hrs after coitus	

♀= female ♂= male, * scheduling guidance for participants who are amenorrhoeic can be found in the SSP Manual

Note: *All follow-up visits should be scheduled, ideally, on dates when the female participant is not on her menses. If a study visit does occur during menses all feasible visit procedures should be performed, however visits may be rescheduled at the discretion of the clinician.*

Table 6: Group 1- Visit 1: Screening- No Gel/No Coitus Visit Procedures

Group 1 Visit 1: Screening No Gel/No Coitus Visit Procedures			
Component		**Female Participants**	**Male Participants**
Administrative and Regulatory		• Informed consent • Informed consent comprehension assessment • Assess eligibility • Assign participant identification (PTID) number • Collect locator information • Collect demographic information • Reimbursement • Schedule next visit, if indicated	• Informed consent • Informed consent comprehension assessment • Assess eligibility • Assign PTID • Collect locator information • Collect demographic information • Reimbursement • Schedule next visit, if indicated
Clinical		• Collect medical and menstrual history • Collect concomitant medication history • Perform a physical exam • Perform a pelvic exam • Disclose available test results • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated	• Collect medical history • Collect concomitant medication history • Perform a physical exam • Perform a genital exam • Disclose available test results • Collect a semen sample (baseline) • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated
Behavioral/ Counseling		• Provide counseling: – HIV pre- post- test – HIV/STI risk reduction – Contraceptive	• Provide counseling: – HIV pre- post- test – HIV/STI risk reduction
Laboratory	**Urine**	• hCG • Urine NAAT for GC/CT • Urine culture, if indicated	• Urine NAAT for GC/CT • Urine culture, if indicated
	Blood	• CBC with platelets • HIV-1 serology • Syphilis serology • HBsAg	• HIV-1 serology • Syphilis serology • HBsAg
	Vaginal/ Cervical/ Penile	• Vaginal fluid pH • Rapid Trichomonas test • KOH wet mount for candidiasis, if indicated • Wet mount for BV, if indicated • Cervical specimen for pap smear, if indicated • CVL for PD	

Note: The screening semen sample from the male partner will be used to assess the typical semen biomarker value for each male participant so that the volume of ejaculate can be assessed using the CVL. This data will inform any change in drug concentration or activity observed in the post-coital samples.

7.3 Group 1 (Single Dose/BAT Cohort) – Enrollment and Study Follow-up Visits

Approximately 2-3 days after the final day of the female participants' menses (cessation of bleeding) following the Screening Visit, couples will return to the clinic for Visit 2 (Enrollment- No Gel/Coitus). Scheduling guidance for participants who are amenorrhoeic can be found in the SSP Manual. Participants will receive coital visit instructions which will include information regarding when participants should return to the study clinic (no more than 2 hours after completing the coital act) and other

information to ensure participants comply with study requirements. The couple will then engage in coitus at a local hotel or similar location. Female participants will return to the clinic after completing the coital act for post-Coitus sampling procedures at Visit 2b (Post-Coital Sampling).

Approximately 3-7 days following Visit 2b (Post-Coital Sampling), the couple will return for Visit 3a (Gel -1hr/Coitus). Female participants will be provided study product for application at the hotel or comparable location. Participants will receive coital visit instructions which will include information regarding the timing of study product application (1 hour prior to coitus), when participants should return to the study clinic (no more than 2 hours after completing the coital act), and other information to ensure participants comply with study requirements. Participants will insert the study product approximately 1 hour prior to coitus. Participants will then engage in coitus and female participants will return to the clinic no more than 2 hours after completing the coital act and undergo post-sex sampling procedures at Visit 3b (Post-Coital Sampling).

After a minimum 10-day washout period, females will return to the clinic for Visit 4a (Gel -1hr/ No Coitus), female participants insert a single dose of gel. Sampling procedures will occur at a similar time to those taken at Visit 3b (Post-Coital Sampling).

After a minimum 10-day washout period, couples will return to the clinic for Visit 5a (Gel -24hr/Coitus), females participants insert a single dose of gel vaginally 24 hours prior to engaging in coitus. Participants will receive coital visit instructions which will include information regarding the timing of study product application (24 hours prior to sex), when participants should return to the study clinic (no more than 2 hours after completing the coital act), and other information to ensure participants comply with study requirements. Sampling procedures will occur approximately 2 hours after coitus at Visit 5b (Post-Coital Sampling).

Following a 10-day minimum washout period, the female participant will return to the clinic for Visit 6a (Gel -24/No Coitus). She will apply one applicator of tenofovir 1% gel in the clinic and will return to the clinic approximately 24 hours later for Visit 6b-Sampling.

Following a minimum 10-day washout period, couples will return for Visit 7a/b (Gel -1/Coitus/ Gel +1), females will insert into the vagina the content of one applicator of tenofovir 1% gel approximately 1 hour prior to engaging in coitus and approximately 1 hour after coitus. Both doses of the study product will be vaginally inserted at the location where coitus is to occur (hotel or comparable site). Sampling procedures will occur approximately 2 hours after coitus at Visit 7b (Post-Coital Sampling/ Final Clinic). Male partners will be asked to attend Visit 7b (Post-Coital Sampling/ Final Clinic) as well. Study visit instructions will be provided to participants.

Table 7: Group 1- Visit 2a: Enrollment No Gel/Coitus, Visit 3a: Gel -1/Coitus, Visit 4a: Gel-1 /No Coitus, Visit 5a: Gel -24/Coitus, Visit 6a: Gel -24/No Coitus, Visit 7a: Gel -1/Coitus/ Gel +1

Group 1 **Visit 2a: Enrollment No Gel/Coitus, Visit 3a: Gel -1/Coitus, Visit 4a: Gel-1 /No Coitus, Visit 5a: Gel -24/Coitus, Visit 6a: Gel -24/No Coitus, Visit 7a: Gel -1/Coitus/ Gel +1**			
Component		**Female Participants**	**Male Participants**
Administrative and Regulatory		• Assess eligibility∆ • Eligibility confirmation∆ • Eligibility to continue study participation, including continued monogamy▲ • Provision of coitus visit instructions◘ • Update locator information • Provide reimbursement • Schedule next visit or contact, if indicated	• Assess eligibility ∆ • Eligibility confirmation∆ • Eligibility to continue study participation, including continued monogamy (Do not repeat at enrollment)◘ • Provision of coitus visit instructions◘ • Update locator information◘ • Provide reimbursement ◘ • Schedule next visit or contact, if indicated◘
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Perform a modified physical exam • Perform pelvic exam∆, if indicated • Offer panty liners • Disclose available test results • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated	• Review/update medical history◘ • Review/update concomitant medications◘ • Perform a modified physical exam◘ • Perform genital exam∆, if indicated◘ • Disclose available test results◘ • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated◘
Behavioral/Counseling		• Conduct behavioral assessment∆ • Provide contraceptive counseling • Provide modified HIV/STI risk reduction counseling	• Conduct behavioral assessment∆ • Provide modified HIV/STI risk reduction counseling◘
Laboratory	**Urine**	• hCG • Urine culture, if indicated • Urine NAAT for GC/CT, if indicated	• Urine culture, if indicated◘ • Urine NAAT for GC/CT, if indicated◘
	Vaginal/ Cervical	• Vaginal fluid pH • Rapid Trichomonas test, if indicated • KOH wet mount for candidiasis, if indicated • Wet mount for BV, if indicated	
	Blood	• Plasma archive∆	• Plasma archive∆
Study Product Supply		• Provision of study product▲ • Study product use instructions ▲	

∆ Visit 2a only, ◘ Visit 2a, 3a, 5a,7a only, ▲ Visit 3a, 4a, 5a, 6a, 7a only

Table 8: Group 1- Visit 2b: Post-Coital Sampling, Visit 3b: Post-Coital Sampling, Visit 4b: Sampling, Visit 5b: Post-Coital Sampling, Visit 6b: Sampling

Group 1 Visit 2b: Post-Coital Sampling, Visit 3b: Post-Coital Sampling, Visit 4b: Sampling, Visit 5b: Post-Coital Sampling, Visit 6b: Sampling		
Component		**Female Participant Procedures**
Administrative and Regulatory		• Provide reimbursement • Schedule next visit or contact, if indicated • Collect coitus visit data◘
Clinical		• Record/update AEs • Perform pelvic exam
Behavioral/Counseling		• Conduct behavioral assessment▲
Laboratory	**Blood**	• PK ▲
	Vaginal/ Cervical	• Vaginal fluid pH • CVL – PK▲ – PD – Semen biomarker◘ • Vaginal and cervical biopsies▲ – PK • Cervical cytobrush▲ – PK
	Rectal	• Rectal sponge▲ – PK
Study Product Supply		• Collect used applicator/unused study product (if any)▲

◘ Visit 2b, 3b, 5b only, ▲ Visit 3b, 4b, 5b, 6b only

7.3.1 Group 1 – Visit 7b: Post-Coital Sampling/ Final Clinic Visit

The following procedures will occur approximately 2 hours after the coital episode.

Table 9: Group 1- Visit 7b: Post-Coital Sampling/ Final Clinic Visit*

Group 1 Visit 7b: Post-Coital Sampling/ Final Clinic Visit* Male and Female Procedures		
Component	**Female Participants**	**Male Participants**
Administrative and Regulatory	• Provide reimbursement • Schedule next visit or contact, if indicated • Collect coitus visit data	• Provide reimbursement • Schedule next visit or contact, if indicated
Clinical	• Perform a modified physical examination, if indicated* • Perform pelvic exam • Disclose available test results, if indicated* • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated • Record/update AEs	• Perform a modified physical examination, if indicated* • Perform genital exam • Disclose available test results, if indicated* • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated • Record/update AEs
Behavioral/Counseling	• Conduct behavioral assessment • Conduct acceptability assessment • Provide counseling: – HIV pre- post- test – HIV/STI risk reduction	• Conduct behavioral assessment • Conduct acceptability assessment • Provide counseling: – HIV pre- post- test – HIV/STI risk reduction

Group 1 Visit 7b: Post-Coital Sampling/ Final Clinic Visit* Male and Female Procedures			
Component		**Female Participants**	**Male Participants**
Laboratory	**Urine**	• Urine culture, if indicated • Urine NAAT for GC/CT, if indicated	• Urine culture, if indicated • Urine NAAT for GC/CT, if indicated
	Blood	• HIV-1 serology • PK	• HIV-1 serology
	Vaginal/ Cervical	• Vaginal fluid pH • Rapid Trichomonas test, if indicated • KOH wet mount for candidiasis, if indicated • Wet mount for BV, if indicated • CVL – PK – PD – Semen biomarker • Vaginal and cervical biopsies – PK • Cervical cytobrush PK	
	Rectal	• Rectal sponge PK	
Study Product		• Collect used applicator/unused study product (if any)	

* Note: Study staff will make arrangements with participants to provide test results not immediately available at the Final Clinic Visit/Early Termination Visit, such as HIV test results and test results from any unresolved AE. In addition, standard referrals will also be provided at the time of results dissemination, if applicable.

7.4 Group 2 (Multiple Dose Cohort)- Screening Visit (Visit 1)

A Screening Visit may take place up to 30 days prior to the Enrollment Visit. Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed consent for screening will be obtained before any screening procedures are initiated. Both the female and the male must meet the eligibility requirements for the couple to be eligible. For participants who do not meet the eligibility criteria (e.g., STI or HIV-positive, self-reported non-monogamy, etc.), screening will be discontinued for the couple once ineligibility is determined.

All test results will be provided to an individual participant in a private room to ensure participant confidentiality. If a participant is found to be ineligible based upon STI or HIV status study staff will not inform the infected participant's partner. Participants may choose to disclose this information on their own. Study staff will comply with local requirements to report communicable diseases including HIV-1 identified among study participants to health authorities.

In addition, if one partner admits to non-monogamy, study staff will inform the couple that they are ineligible for the study; however non-monogamy will not be disclosed to the couple as the reason for ineligibility.

All individuals who come to the clinic for Screening will be provided counseling regarding HIV/STI prevention, see Table 11. Participants will be informed that condoms are the only known way to prevent HIV and other STIs.

Note: Participants may rescreen a total of one time; however both the female and male participants must meet the eligibility requirements at the time of the screening.

Table 10: Group 2- Multiple Dose Cohort Study Visit Schedule

Group 2- Multiple Dose Cohort				
Gel	**Visit**	**Visit Name**	**Targeted Visit Schedule**	**Coitus**
	1 ♂♀	Screening (Baseline CVL)		
	2 ♂♀	Enrollment- Provision of Study Product	To occur ~2-3 days following the final day of the female participant's period*	
-1 hr	3a ♂♀	Gel -1/Coitus	To occur 6 days after Visit 2	X
	3b ♀	Post-Coital Sampling	To occur ~2 hrs after coitus	
	4 ♀	Provision of Study Product	To occur after a min. 20 day washout period	
	5 ♀	Sampling	To occur at similar time relative to sampling at Visit 3b	
-72 hr	6 ♀	Provision of Study Product	To occur after a min. 20 day washout period	
	7a ♂♀	Gel -72/Coitus	To occur 9 days after Visit 6	X
	7b ♀	Post-Coital Sampling	To occur ~2 hrs after coitus	
	8 ♀	Provision of Study Product	To occur after a min. 20 day washout period	
	9/ Final ♂♀	Sampling	To occur at similar time relative to sampling at Visit 7b	

♀= female ♂= male, * scheduling guidance for participants who are amenorrhoeic can be found in the SSP Manual.

Note: All follow-up visits should be scheduled, ideally, on dates when the female participant is not on her menses. If a study visit does occur during menses all feasible visit procedures should be performed, however visits may be rescheduled at the discretion of the clinician.

Table 11: Group 2- Visit 1: Screening

Group 2 Visit 1: Screening Procedures for Males and Females		
Component	**Female Participants**	**Male Participants**
Administrative and Regulatory	• Informed consent • Informed consent comprehension assessment • Assess eligibility • Assign PTID • Collect locator information • Collect demographic information • Provide reimbursement • Schedule next visit, if indicated	• Informed consent • Informed consent comprehension assessment • Assess eligibility • Assign PTID • Collect locator information • Collect demographic information • Provide reimbursement • Schedule next visit, if indicated

Group 2 Visit 1: Screening Procedures for Males and Females			
Component		**Female Participants**	**Male Participants**
Clinical		• Collect medical and menstrual history • Collect concomitant medication history • Perform a physical exam • Perform a pelvic exam • Disclose available test results • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated	• Collect medical history • Collect concomitant medication history • Perform a physical exam • Perform a genital exam • Disclose available test results • Collect a semen sample (baseline) • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated
Behavioral/ Counseling		• Provide counseling: – HIV pre- post- test – HIV/STI risk reduction – Contraceptive	• Provide counseling: – HIV pre- post- test – HIV/STI risk reduction
Laboratory	**Urine**	• hCG • Urine NAAT for GC/CT • Urine culture, if indicated	• Urine NAAT for GC/CT • Urine culture, if indicated
	Blood	• CBC with platelets • HIV-1 serology • Syphilis serology • HBsAg	• HIV-1 serology • Syphilis serology • HBsAg
	Vaginal/ Cervical/ Penile	• Vaginal fluid pH • Rapid Trichomonas test • KOH wet mount for candidiasis, if indicated • Wet mount for BV, if indicated • Cervical specimen for pap smear, if indicated • CVL – PD	

Note: The screening semen sample from the male partner will be used to assess the typical semen biomarker value for each male participant so that the volume of ejaculate can be assessed using the CVL. This data will inform any change in drug concentration or activity observed in the Post-Coital samples.

7.5 Group 2 (Multiple Dose Cohort) – Enrollment and Study Follow-up Visits

Approximately 2-3 days after the final day of the female participants' menses (cessation of bleeding) following the Visit 1 (Screening Visit), see SSP Manual for guidance for participants who are amenorrhoeic, couples will return to the clinic for Visit 2 (Enrollment/Provision of Product). Female participants will apply the first dose vaginally and will receive product provision sufficient to allow for the next 5 daily doses at home (doses 2-6).

At Visit 3a (Gel -1/Coitus), following a 6-day regimen of product, couples will return to the clinic at which time the 7th dose of product will be provided for application by the female participant at the location where sex is to occur (hotel or comparable site), to be applied approximately 1 hour prior to coitus. Prior to the coital visit, participants will receive coital visit instructions, these instructions will include information regarding the timing of study product application (approximately 1 hour prior to coitus), when participants should return to the study clinic (no more than 2 hours after completing the coital act), and other information to ensure participants comply with study requirements.

Participants will then engage in coitus and female participants will return to the clinic to undergo post-coital sampling procedures at Visit 3b (Post-Coital Sampling).

After a minimum 20 day washout period female participants will return to the clinic, for Visit 4. At Visit 4 (Provision of Study Product), female participants will apply the first of the 7 daily doses of gel at the clinic and receive a study product provision sufficient to allow for the next 5 daily doses at home (doses 2-6).

At Visit 5 (Sampling), female participants will return to the clinic to insert the 7^{th} dose and undergo sampling procedures at a time-point matched to that of Visit 3b (Post-Coital Sampling Visit).

After a minimum 20 day washout period, the female participant will return for Visit 6 (Provision of Study Product), and will apply the first of 7 daily doses of gel at the clinic and receive a study product provision sufficient to allow for the next 6 daily doses at home (doses 2-7).

At Visit 7a (Gel -72/Coitus), following a 7-day regimen of product, couples will return to the clinic to engage in coitus approximately 72 hours after the female participant's last dose of product. Again, prior to the coital visit, participants will receive coital visit instructions, these instructions will include information regarding when participants should return to the study clinic (not to exceed 2 hours after completing the coital act), and other information to ensure participants comply with study requirements. Participants will then engage in coitus and female participants will return to the clinic undergo post-coital sampling procedures at Visit 7b (Post-Coital Sampling).

After a minimum 20 day washout period, the female participant will return to the clinic for Visit 8 (Provision of Study Product), she will apply the first of the 7 daily doses of gel at the clinic and receive a study product provision sufficient to allow for the next 6 daily doses at home (doses 2-7).

At Visit 9 (Sampling), the couple returns the clinic after the female participant has administered the final dose of gel approximately 72 hours prior to the visit. Participants will return to the clinic and the female participant will undergo sampling procedures for the final time.

Table 12: Group 2- Visit 2: Enrollment- Provision of Study Product, Visit 4: Provision of Study Product, Visit 6: Provision of Study Product, Visit 8: Provision of Study Product

Group 2 Visit 2- Enrollment: Provision of Study Product, Visit 4: Provision of Study Product, Visit 6: Provision of Study Product, Visit 8: Provision of Study Product			
Component		**Female Participants**	**Male Participants**
Administrative and Regulatory		• Assess eligibility Δ • Eligibility confirmationΔ • Eligibility to continue study participation, including continued monogamy◊ • Update locator information • Provide reimbursement • Schedule next visit, if indicated	• Assess eligibility Δ • Eligibility confirmationΔ • Update locator informationΔ • Provide reimbursementΔ • Schedule next visit, if indicatedΔ
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Disclose available test results • Offer panty liners • Perform a modified physical examination Δ • Record/update AEs◊ • Perform pelvic examΔ, if indicated • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated	• Review/update medical historyΔ • Review/update concomitant medicationsΔ • Disclose available test resultsΔ • Perform a modified physical examination Δ • Perform genital examΔ • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicatedΔ
Behavioral/ Counseling		• Conduct behavioral assessmentΔ • Provide contraceptive counseling • Provide modified HIV/STI risk reduction counseling • Provide adherence counseling	• Conduct behavioral assessmentΔ • Provide modified HIV/STI risk reduction counseling Δ
Laboratory	**Urine**	• hCG • Urine NAAT for GC/CT, if indicated • Urine culture, if indicated	
	Vaginal/ Cervical	• Vaginal fluid pH • Rapid Trichomonas test, if indicated • KOH wet mount for candidiasis, if indicated • Wet mount for BV, if indicated	
	Blood	• Plasma archiveΔ	• Plasma archiveΔ
Study Product Supply		• Provision of study product • Study product use instructions	

Δ To be collected at Visit 2 only, ◊=Visits 4, 6, and 8

Table 13: Group 2- Visit 3a: Gel -1/Coitus, Visit 7a: Gel -72/Coitus

Group 2 Visit 3a: Gel -1/Coitus, Visit 7a: Gel -72/Coitus Male and Female Procedures		
Component	**Female Participants**	**Male Participants**
Administrative and Regulatory	• Eligibility to continue study participation, including continued monogamy • Update locator information • Provision of coitus visit instructions • Provide reimbursement • Schedule next visit or contact, if indicated	• Eligibility to continue study participation, including continued monogamy • Update locator information • Provide reimbursement • Schedule next visit or contact, if indicated • Provision of coitus visit instructions

Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Perform modified physical exam • Perform pelvic exam, if indicated • Offer panty liners • Disclose available test results • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated • Record/update AEs	• Review/update medical history • Review/update concomitant medications • Perform modified physical exam • Perform genital exam, if indicated • Disclose available test results • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated
Behavioral/Counseling		• Provide contraceptive counseling • Provide modified HIV/STI risk reduction counseling • Provide adherence counseling	• Provide modified HIV/STI risk reduction counseling
Laboratory	**Urine**	• hCG • Urine culture, if indicated • Urine NAAT for GC/CT, if indicated	• Urine culture, if indicated • Urine NAAT for GC/CT, if indicated
	Vaginal/ Cervical	• Vaginal fluid pH • Rapid Trichomonas test, if indicated • KOH wet mount for candidiasis, if indicated • Wet mount for BV, if indicated	
Study Product Supply		• Provision of study product • Study product use instructions • Collect all used applicators/unused study product	

Table 14**: Group 2- Visit 3b: Post-Coital Sampling, Visit 5: Sampling, Visit 7b: Post-Coital Sampling**

Group 2 **Group 2- Visit 3b: Post-Coital Sampling, Visit 5: Sampling, Visit 7b: Post-Coital Sampling**		
Component		**Female Participants**
Administrative and Regulatory		• Provide reimbursement • Schedule next visit or contact, if indicated • Collect coitus visit data◘ • Eligibility to continue study participation, including continued monogamy ◊ • Update locator information ◊
Clinical		• Perform pelvic exam • Record/update AEs • Review/update medical and menstrual history◊ • Review/update concomitant medications◊
Behavioral/Counseling		• Conduct a behavioral assessment • Product adherence assessment • Provide contraceptive counseling◊
Laboratory	**Urine**	• hCG ◊
	Blood	• PK
	Vaginal/ Cervical	• Vaginal fluid pH • CVL – PK – PD – Semen biomarker • Vaginal and cervical biopsies – PK • Cervical cytobrush – PK

	Rectal	• Rectal Sponge – PK
Study Product Supply		• Collect all used applicators/unused study product

◘ To be performed at Visit 3b and 7b only. ◊= Visit 5 only

7.5.1 Group 2- Visit 9: Sampling/Final Clinic Visit*

Table 15: Group 2- Visit 9: Sampling/Final Clinic Visit*

Group 2 Visit 9- Sampling/ Final Clinic Visit* Male and Female Procedures			
Component		**Female Participants**	**Male Participants**
Administrative and Regulatory		• Provide reimbursement • Schedule next visit or contact, if indicated	• Provide reimbursement • Schedule next visit or contact, if indicated
Clinical		• Review/update medical and menstrual history • Review/update concomitant medications • Perform a modified physical examination • Perform pelvic exam • Disclose available test results, if indicated* • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated • Record/update AEs	• Review/update medical history • Review/update concomitant medications • Perform a modified physical examination • Perform genital exam • Disclose available test results, if indicated* • Treat or prescribe treatment for UTI/RTI/STIs or refer, if indicated • Record/update AEs
Behavioral/Counseling		• Conduct behavioral assessment • Conduct acceptability assessment • Provide counseling: – HIV pre- post- test – HIV/STI risk reduction	• Conduct behavioral assessment • Conduct acceptability assessment • Provide counseling: – HIV pre- post- test – HIV/STI risk reduction
Laboratory	**Urine**	• hCG • Urine culture, if indicated • Urine NAAT for GC/CT, if indicated	• Urine culture, if indicated • Urine NAAT for GC/CT, if indicated
	Blood	• PK • HIV-1 serology	• HIV-1 serology
	Vaginal/ Cervical	• Vaginal fluid pH • Rapid Trichomonas test, if indicated • KOH wet mount for candidiasis, if indicated • Wet mount for BV, if indicated • CVL – PK – PD – Semen biomarker • Vaginal and cervical biopsies – PK • Cervical cytobrush – PK	
	Rectal	• Rectal sponge – PK	
Study Product		• Collect used applicator/unused study product (if any)	

* Note: Study staff will make arrangements with participants to provide test results not immediately available at the Final Clinic Visit/Early Termination Visit. In addition, standard referrals will also be provided at the time of results dissemination, if applicable.

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

If a participant or their study partner permanently discontinues gel use both individuals will be terminated from the study and female participants will be instructed to return any remaining unused study gel (Group 2 only).

Note: IoR discretion will be used for participants suspected of non-monogamy.

7.6.1 Participants Who Become Infected with HIV-1 or Sexually Transmitted Infections

Male or female participants who become infected with an STI will receive care or be referred for treatment and participants who become infected with HIV-1 will be referred for treatment according to the local standard of care. Female participants will be permanently discontinued from gel use and will be instructed to return the study gel (Group 2 only) or staff will retrieve the product. HIV RNA and HIV drug resistance testing will be done on those participants who become infected with HIV. Results will be provided when they become available**.** Study staff, with written permission from the participant, may contact the medical care provider to inform him/her of the participant's involvement in MTN-011. The participant as well as their participating partner will be terminated from the study.

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

7.6.2 Participants Who Become Pregnant

Participants who become pregnant will be permanently discontinued from study product use and they, along with their participating partner, will be terminated from the study. Participants in Group 2 of the study will be instructed to return the study gel. (See Sections 8.5 and 9.7 for further details.)

Participants who become pregnant while on study may be offered enrollment in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study, (www.mtnstopshiv.org/), provided their study site is participating in MTN-016.

In addition, study staff will make every effort to maintain contact with a participant who is pregnant prior to the study end date or is found to be pregnant at the Final Clinic Visit/Early Termination Visit to ascertain the participant's pregnancy outcome (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Study sites may complete the final contact visit(s) at the study site or at

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

7.6.3 Participants Who are Found to be Non-monogamous

Male or female participants who self-report non-monogamy after enrollment will be terminated from the study. The participating partner will also be terminated from the study. If a female participant reports non-monogamy at a clinic visit or if a male partner reports non-monogamy at a visit (interim) in which their partner is not present, every effort will be made to schedule an Early Termination Visit as soon as possible with the other partner.

See additional information about study product retrieval in Section 6.6.

7.7 Interim Visits

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the study. All interim contacts and visits will be documented in participants' study records and on applicable case report forms.

Some Interim Visits may occur for administrative reasons. For example, the participant may have questions for study staff or Group 2 participants may require additional study supplies. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care. All interim contacts and visits will be documented in participants' study records and on applicable case report forms (CRFs).

7.8 Pharmacokinetic and Pharmacodynamic Sampling Schedule

Table 16: Pharmacokinetic Specimen Collection Schedule

Specimens	PK Specimen Collection for Group 1 Female Participants
	Group 1 Visits
Cervicovaginal lavage	– Visit 3b: Post-Coital Sampling – Visit 4b: Sampling – Visit 5b: Post-Coital Sampling – Visit 6b: Sampling – Visit 7b: Post-Coital Sampling/Final Clinic Visit
Tissue biopsies (vaginal and cervical)	– Visit 3b: Post-Coital Sampling – Visit 4b: Sampling – Visit 5b: Post-Coital Sampling – Visit 6b: Sampling – Visit 7b: Post-Coital Sampling/Final Clinic Visit
Cervical Cytobrush	– Visit 3b: Post-Coital Sampling – Visit 4b: Sampling – Visit 5b: Post-Coital Sampling – Visit 6b: Sampling – Visit 7b: Post-Coital Sampling/Final Clinic Visit
Blood	– Visit 3b: Post-Coital Sampling – Visit 4b: Sampling – Visit 5b: Post-Coital Sampling – Visit 6b: Sampling – Visit 7b: Post-Coital Sampling/Final Clinic Visit
Rectal sponge	– Visit 3b: Post-Coital Sampling – Visit 4b: Sampling – Visit 5b: Post-Coital Sampling – Visit 6b: Sampling – Visit 7b: Post-Coital Sampling/Final Clinic Visit
Specimens	**PK Specimen Collection for Group 2 Female Participants**
	Group 2 Visits
Cervicovaginal lavage	– Visit 3b: Post-Coital Sampling – Visit 5: Sampling – Visit 7b: Post-Coital Sampling – Visit 9: Sampling/ Final Clinic Visit
Tissue biopsies (vaginal and cervical)	– Visit 3b: Post-Coital Sampling – Visit 5: Sampling – Visit 7b: Post-Coital Sampling – Visit 9: Sampling/ Final Clinic Visit
Cervical Cytobrush	– Visit 3b: Post-Coital Sampling – Visit 5: Sampling – Visit 7b: Post-Coital Sampling – Visit 9: Sampling/ Final Clinic Visit
Blood	– Visit 3b: Post-Coital Sampling – Visit 5: Sampling – Visit 7b: Post-Coital Sampling – Visit 9: Sampling/ Final Clinic Visit
Rectal sponge	– Visit 3b: Post-Coital Sampling – Visit 5: Sampling – Visit 7b: Post-Coital Sampling Visit 9: Sampling/ Final Clinic Visit

Table 17: Pharmacodynamic Specimen Collection Schedule

Specimens	PD Specimen Collection for Group 1 Female Participants Group 1 Visits
Cervicovaginal lavage	– Visit 2b: Sampling – Visit 3b: Post-Coital Sampling – Visit 4b: Sampling – Visit 5b: Post-Coital Sampling – Visit 6b: Sampling – Visit 7b: Post-Coital Sampling/Final Clinic Visit
Specimens	**PD Specimen Collection for Group 2 Female Participants** **Group 2** **Visits**
Cervicovaginal lavage	– Visit 3b: Post-Coital Sampling – Visit 5: Sampling – Visit 7b: Post-Coital Sampling – Visit 9: Sampling/ Final Clinic Visit

7.9 Behavioral Measures

The quantitative instrument will be structured around the following topics:

- Behavioral Assessment- Sexual and other behaviors (including prohibited sexual behavior and prohibited practices)
- Product adherence (Group 2 only)
- Protocol and product acceptability

7.9.1 Behavioral Assessment- Sexual and Other Behaviors

Key sexual behavior and other behaviors (including prohibited practices for protocol adherence) will be captured by standardized assessments. This assessment will be modeled on the sexual behavior and other behavior assessments being conducted in MTN-013 (www.mtnstopshiv.org/).

7.9.2 Product Adherence

For participants enrolled in Group 2, key product adherence measures will be captured by standardized assessment. Study staff will provide participants with guidance on strategies to optimize recall of relevant behavioral and adherence data. This quantitative assessment will be modeled on the adherence assessment for MTN-007 and MTN-008 (www.mtnstopshiv.org/). A reminder system is planned for this group during the home dosing phase, consisting of either daily reminder phone or text messages.

Participants in both groups will be asked to return all applicators (used and unused).

7.9.3 Protocol and Product Acceptability Assessment

At the Final Clinic Visit, participants will receive a standardized assessment, which will include questions regarding their experience with trial participation, and whether or not

the participant would be willing to take part in a trial of similar design in the future. They will also be asked about the acceptability of and experience with using the gel.

7.10 Clinical Evaluations and Procedures

Physical Examination
Physical examination will include the following assessments:

- General appearance
- Vital signs
  - Temperature
  - Pulse
  - Blood pressure
  - Respirations
- Genitourinary
- Weight*
- Height*
- Abdomen*
- Heart*
- Lungs*
- Extremities*
- Skin*

*may be omitted after the Screening Visit

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

Pelvic and Genital Examinations
Pelvic examinations will be conducted per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at http://www.conrad.org/assets/attachments/Revised_Manual.PDF. The required sequence of procedures and specimen collection performed during pelvic exams will be specified in the MTN-011 SSP Manual.

The male genital examination should include a general inspection via naked eye and, if necessary, a hand-held magnifying glass of the following:

- Entire penile surface
  - Glans
  - Urethral meatus
  - Internal and external foreskin (if present)
  - Shaft
- Scrotum

- Inguinal lymph nodes

7.11 Laboratory Evaluations

Local Laboratory

- Urine
  - hCG
  - Chlamydia and gonorrhea
- Blood
  - Syphilis
  - HIV serology
  - CBC and platelets
  - HBsAg
- Vaginal
  - pH
  - Rapid test for Trichomonas
- Cervical
  - Pap smear interpretation

Network Laboratory

- Blood
  - Plasma archive
  - Tenofovir levels (NL Pharmacology Core)
- Vaginal
  - Biopsy tenofovir levels (NL Pharmacology Core)
- Cervical
  - Biopsy tenofovir levels (NL Pharmacology Core)
  - Cytobrush for tenofovir levels (NL Pharmacology Core)
- Cervical/Vaginal
  - CVL tenofovir levels (NL Pharmacology Core)
  - CVL antiviral assay
  - CVL semen biomarker
- Rectal
  - Sponge tenofovir levels (NL Pharmacology Core)
- Semen
  - Semen biomarker

7.12 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical laboratory practice, the MTN Network Laboratory Manual (www.mtnstopshiv.org/), in accordance with current DAIDS Laboratory Requirements, MTN-011 Study Specific Procedures Manual (www.mtnstopshiv.org/), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented

when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

7.13 Specimen Handling

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

7.14 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and 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 (MO), Protocol Safety Physicians, CONRAD Safety Physicians, and SCHARP Clinical Affairs Safety Associates will serve as the PSRT. The MTN Statistical Data 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. The content, format, and frequency of the safety data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation.

8.2 Clinical Data and Safety Review

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

MTN SDMC Clinical Affairs staff will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification.

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 transmission and medical ethics may be invited to join the PSRT safety review. A recommendation to pause or stop the trial may be made by the PSRT at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

If the protocol team has serious safety concerns they will request a review of data by the Study Monitoring Committee (SMC). SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Members of the SMC will be independent investigators with no interest (financial or otherwise) in the outcomes of this study. If at any time a decision is made to discontinue enrollment and/or study product use in all participants, CONRAD will notify the FDA and the Clinical Research Site (CRS) Principal Investigator will notify the responsible IRB expeditiously.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant exposed to 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 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 enrolled participants beginning at the time of eligibility checklist completion and final sign-off. The term “investigational product” for this study refers to all study products, see Section 8.4.2.

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

Study site staff will document in source documents all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. Study staff also will report on CRFs the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs
  - Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs
  - Genital bleeding clinically assessed to be expected is not an AE
- All AEs of severity Grade 2 or higher
- All serious AEs, as defined by the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities specified in the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004(clarification August 2009), that are not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements per Section 8.4 below

The current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (clarification dated August 2009), Addenda 1 (Female Genital Table for Use in Microbicide Studies) and 2 (Male Genital Grading Table for Use in Microbicide Studies) will be the primary tools for grading adverse events for this protocol, except that asymptomatic BV will not be a reportable AE. Adverse events not included in that table will be graded by the DAIDS AE Grading Table, Version 1.0 December 2004 (Clarification dated August 2009). In cases where an AE is covered in multiple tables, Addenda 1 and 2 (Female Genital and Male Genital Grading Table for Use in Microbicide Studies) will be the grading scales utilized for women and men, respectively.

8.3.2 Serious Adverse Events

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

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life-threatening, or require hospitalization but may jeopardize the participant or require intervention to prevent one of the outcomes listed in the definition above.

8.3.3 Adverse Event Relationship to Study Product

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

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

8.4 Expedited Adverse Event Reporting Requirements

8.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/. The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

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

EAE reporting procedures specific to this protocol are that once the sites have submitted EAEs via DAERS (as above), the RSC Safety Office will also prepare the draft safety reports and send them to the CONRAD and DAIDS MOs for review.

Study sites will be contacted by the DAIDS MO if any further information or clarification is needed after the report is evaluated by CONRAD and DAIDS MO. The RSC Safety Office will then prepare the final report which will go to CONRAD for signature and submission to the FDA. Copies of this final report will be filed with CONRAD and RSC. Additionally, the RSC Safety Office will distribute safety reports to all DAIDS sites that use products under investigation in this study.

For all EAEs submitted, sites must file an RSC update with the final or stable outcome unless the initial EAE submitted had a final or stable outcome noted already.

8.4.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in the Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, January 2010 will be used for this study.

- The study agents for which expedited reporting to CONRAD and the DAIDS MO are required are: tenofovir 1% gel and the gel applicator.

8.4.3 Grading Severity of Events

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (clarification dated August 2009), Addenda 1 (Female Genital Table for Use in Microbicide Studies) and 2 (Male Genital Grading Table for Use in Microbicide Studies) will be used and are available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/. Adverse events not included in these tables will be graded by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (clarification dated August 2009). In cases where an AE is covered in all tables, the DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification dated August 2009), Addendum 1 (Female Genital Table for Use in Microbicide Studies) will be the grading scale utilized for women and Addendum 2 (Male Genital Grading Table for Use in Microbicide Studies) will be the grading scale utilized for men.

8.4.4 Expedited AE Reporting Period

The expedited AE reporting period for this study is as defined in Version 2.0 of the EAE Manual.

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

8.5 Pregnancy and Pregnancy Outcomes

Pregnant participants are excluded from this study. Routine urine testing is performed at every study visit. If participants become pregnant at any time during the course of the study permanent discontinuation of study product will result. Pregnant participants, along with their participating partner, will be terminated from the study, as per Section 7.6.2.

Pregnancy-related data will be collected using the pregnancy CRFs for all pregnancies detected during the study. Pregnancy outcomes will not be expeditiously reported to CONRAD and the DAIDS MO unless there is an associated adverse event in the pregnant participant that meets expedited reporting criteria or the pregnancy results in a congenital anomaly meeting the Manual for Expedited Reported of Adverse Events to DAIDS (Version 2.0, January 2010) guidelines for expedited reporting. Fetal losses without congenital anomalies or maternal complications that require expedited reporting will not be expeditiously reported but data will be captured via the pregnancy CRFs.

After the participant's final study contact, pregnancy outcomes that meet criteria for EAE reporting as described above (e.g., maternal complications, congenital anomalies) occurring among participants known to be pregnant at the Final Study Visit will continue be expeditiously reported. The SDMC will prepare and provide to CONRAD and to the DAIDS MO a quarterly report on all pregnancies and their outcomes. The SDMC will also prepare an annual summary report of all AEs for the annual IND reports (submitted by CONRAD).

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 information in accordance with local regulatory agencies' or other local authorities' requirements. Site IoRs/designees also will submit AE information and any other relevant safety information to their IRBs in accordance with IRB requirements.

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. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. In addition, if it is discovered that a participant has been non-monogamous or found to have an STI or HIV at screening or at any other time during the study, participants may experience social harms. 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. In the event that a participant reports social harm, every effort will be made by study staff to provide

appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Each site will provide such care and counseling in accordance with standardized guidance provided in site SOPs. While maintaining participant confidentiality, study sites may engage their CABs in exploring the social context surrounding instances of social harm.

9 CLINICAL MANAGEMENT

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

9.1 Grading System

AE severity grading is described in Section 8.3.1.

9.2 Dose Modification Instructions

No dose modifications will be undertaken during 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:

- Indeterminate or positive HIV-1 rapid test
- Acquisition of STI
- Male or female participant self-report of non-monogamy
- Pregnancy
- Report of use of PEP for HIV exposure
- Report of use of prohibited concomitant medications as described in Section 6.9
- 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.

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

Grade 1 or 2

In general, a participant who develops a Grade 1 or 2 AE as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (clarification dated August 2009), Addenda 1 (Female Genital Table for Use in Microbicide Studies) and 2 (Male Genital Grading Table for Use in Microbicide Studies) regardless of relationship to study product may continue product use. If the IoR/designee opts to temporarily hold study product, the PSRT must be notified.

Grade 3

Participants who develop a Grade 3 AE as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (clarification dated August 2009), Addenda 1 (Female Genital Table for Use in Microbicide Studies) and 2 (Male Genital Grading Table for Use in Microbicide Studies) that is judged by the IoR/designee to be unrelated to study product may continue product use. If the IoR/designee opts to hold study product, the PSRT will be notified. For participants who develop a Grade 3 AE that is judged by the IoR/designee to be related to product, the PSRT must be consulted to determine if the participant may continue to use product. The IoR/designee would temporary hold study product while awaiting a decision from the PSRT. Assuming product use continues, the IoR/designee must follow-up on this event (unless a different management plan has been devised in consultation with the PSRT):

- Reevaluate the participant at least weekly up to 2 weeks
- Consult the PSRT if the adverse event has not improved to less than or equal to Grade 2 within 2 weeks

Grade 4

A participant who develops a Grade 4 AE as defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (clarification dated August 2009), Addenda 1 (Female Genital Table for Use in Microbicide Studies) and 2 (Male Genital Grading Table for Use in Microbicide Studies) regardless of relationship to study product should have the study product temporarily held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT.

9.5 Other Clinical Events

Management of sexually transmitted infections commonly referred to as STIs and other forms of vaginitis, cervicitis, urethritis will be in accordance with current CDC guidelines (http://www.cdc.gov/std/treatment/). When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible to avoid intravaginal medication use. Incident STIs necessitate termination from study.

If any participant has a symptomatic UTI the participant will be referred for treatment and the visit will be rescheduled after treatment is complete and symptoms have resolved. Further details regarding management of Other Clinical Events will be provided in the SSP (www.mtnstopshiv.org/).

9.6 HIV-1 Infection

If a male or female participant has a positive test for HIV-1, study product must be held for the female participant. See Section 9.3 for additional details.

9.7 Pregnancy

Pregnancy testing will be performed at scheduled study visits and 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 is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Pregnancy outcomes will be reported on relevant CRFs; outcomes meeting criteria for EAE reporting also will be reported on EAE forms.

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

Participants who become pregnant during the course of the study will permanently discontinue study product use and, along with their participating partner, will be terminated from the study.

9.8 Criteria for Early Termination of Study Participation

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

of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is a Phase 1, multi-site, non-randomized, multi-sequence, open-label study. The trial will enroll participants into Single Dose/BAT Cohort (Group 1) and into the Multiple Dose Cohort (Group 2). Couples in Group 1 will be followed for approximately 8 weeks (2 menstrual cycle). Couples in Group 2 will be followed for approximately 14 weeks (3 menstrual cycles).

Group 1
Women in Group 1 will apply a single dose of gel 1 hour prior to coitus at Visit 3a (Gel -1/Coitus). Sampling should occur no more than 2 hours after the coital episode (Visit 3b (Post-Coital Sampling)). After a 10-day washout period (minimum), women will apply a single dose of gel at Visit 4a (Gel -1/No Coitus) without engaging in coitus and have samples collected at Visit 4b (Sampling) at approximately the same time post-gel application as at Visit 3b (Post-Coital Sampling). Women in Group 1 will then apply a single dose of gel 24 hours prior to coitus at Visit 5a (Gel -24/Coitus) and have samples collected at Visit 5b (Post-Coital Sampling). After a minimum 10-day washout period participants will apply a single dose of gel at Visit 6a (Gel -24/No Coitus) without engaging in coitus and have samples collected at Visit 6b (Sampling) at approximately the same time post-gel application as at Visit 5b (Post-Coital Sampling). Finally, women in Group 1, after a final 10-day washout period, will apply a single dose of gel at Visit 7a (Gel -1/Coitus/Gel +1) approximately 1 hour prior to coitus and then engage in sex and apply a second dose of study product approximately 1 hour after coitus. Samples will be collected no more than 2 hours after the coital episode at Visit 7b/Final (Post-Coital Sampling).

Group 2
Women in Group 2 will apply a single dose of gel for seven consecutive days starting at Visit 2 (Enrollment- Provision of Study Product) with the 7th dose applied again 1 hour prior to coitus at Visit 3a (Gel -1/Coitus) and have samples collected at Visit 3b (Sampling). After a minimum 20 day washout period, female participants will receive a provision of study product and will dose for seven consecutive days Visit 4 (Provision of Study Product) with the last dose administered at Visit 5 (Sampling) and samples collected at approximately the same time post-gel application as at Visit 3b (Sampling). Following another minimum 20 day washout period, female participants will apply a single dose of gel for seven consecutive days, starting at Visit 6 (Provision of Study Product) with the 7th dose applied approximately 72 hours before the coital episode at Visit 7a (Gel -72/Coitus). Sampling should occur no more than 2 hours after the coital episode at Visit 7b (Post-Coital Sampling). Another 20 day minimum washout period will occur and female participants will return to the clinic to receive a provision of study product at Visit 8 (Provision of Study Product). Participants will dose for seven consecutive days with the last dose administered 72 hours prior to Visit 9/Final (Sampling) and samples will be collected at approximately the same time post-gel application as at Visit 7b (Post-Coital Sampling).

Participants will be monitored for various adverse events, including all genital, genitourinary, and reproductive system AEs, as specified in Section 8 Assessment of Safety. Clinical management and study product discontinuation guidelines are detailed in Section 9 Clinical Management.

10.2 Study Endpoints

10.2.1 Primary Endpoints

Consistent with the primary study objective to assess the impact of coitus (and semen) on the pharmacokinetics (PK) of tenofovir 1% gel in female genital tract secretions, vaginal and cervical tissue and rectal tract secretions, the following primary endpoints will be assessed:

- **PK.** Tenofovir and tenofovir diphosphate levels (from cellular samples) from cervicovaginal lavage (CVL), cervical cytobrush, tissue biopsies (vaginal and cervical), blood, and rectal sponge following tenofovir 1% gel use in the absence of or following coitus.

Consistent with the primary study objective to assess the impact of coitus (and semen) on pharmacodynamics (PD) of luminal drug by measuring the anti-HIV-1 activity in CVL samples, the following primary endpoint will be assessed:

- **PD.** Anti-HIV-1 activity in CVL

10.2.2 Secondary Endpoints

Consistent with the secondary study objective to assess the acceptability of the MTN -011 trial to male and female participants, the following secondary endpoints will be assessed:

- **Acceptability**. Overall experience with participating in the clinical trial and willingness to participate in a future trial.

10.2.3 Exploratory Endpoints

Consistent with the exploratory objective:

- To determine impact of coitus and/or tenofovir on the genital tract mucosal environment

The following exploratory endpoint will be assessed:

- Measurement of biomarkers of mucosal immunity

Consistent with the exploratory objective:

- To determine whether a semen biomarker can be used to estimate the volume of ejaculate within CVL

The following exploratory endpoint will be assessed:

- Measurement of semen biomarker in ejaculate and in CVL

Consistent with the exploratory objective:

- To assess whether sufficient drug is retained in the lumen in the absence of or following coitus to inhibit HSV-2 as an additional surrogate biomarker of pharmacodynamics

The following exploratory endpoint will be assessed:

- Anti-HSV-2 activity in CVL

10.3 Primary Study Hypothesis

The study hypotheses for the primary objective are:

- Coitus will not impact the pharmacokinetics of TFV following a single precoital dose, BAT or multiple applications of study product

- Coitus will not alter the antiviral activity in genital tract secretions following single precoital dose, BAT or multiple applications of study product

10.4 Sample Size and Power Calculations

The sample size of 40 evaluable couples, with 20 couples in each group (Single Dose /BAT Cohort and Multiple Dose Cohort), was determined with respect to the primary PK endpoints. Details are provided in the section below. Given this sample size, power calculations are also provided for the PD primary endpoint.

10.4.1 Pharmacokinetic Endpoints

Sample size/power formulas for a one-sample, paired t-test, can be used to compute sample size/power. For the primary PK endpoint to assess the impact of coitus on the PK of tenofovir following a single dose and BAT regimen (Group 1), and separately if indicated, following seven daily doses (Group 2), we use data from two studies:

1) a 14-day tenofovir gel study in which CVL TFV levels and anti-HIV-1 activity were measured on Days 3 and 7,[17] and

2) a post-coital study by Keller, et al.[5] which addressed the impact of coitus on the PK of PRO 2000 Gel following a single dose of gel.

From these studies, we estimate the standard deviation of CVL tenofovir data after daily dosing at Days 3 and 7, and the standard deviation for the percentage difference in drug concentration (DC) levels between gel use alone and gel use prior to coitus. We make the assumption that the standard deviation for this percentage difference will be similar for tenofovir 1% gel as it was for PRO 2000 Gel. We also assume that the standard deviation will be similar for the percentage difference due to coitus following seven daily doses as it was for coitus following a single dose.

From the tenofovir 14-day study, we estimated the coefficient of variation (CV) of the gel-only DC levels from CVL at Days 3 and 7 to be 1.2 and 1.1, respectively. From the PRO 2000 Gel study we estimated the mean (SD) percentage change in CVL drug concentration due to the impact of coitus (1-([gel and sex DC] / [gel-only DC]) x 100% for each couple). The mean percentage change was 68% and the standard deviation was 31% (CV of 0.31/0.68=0.5). The gel/sex and gel-only PRO 2000 DC levels yielded CVs of 1.1 and 0.9, respectively. The tenofovir 14-day study produced mean tenofovir DC levels on the same order of magnitude (ng/mL) as seen with the PRO 2000 DC levels in the PRO 2000 post-coital study. For the MTN-011 study, we assume a conservative CV of 1.5 for the mean percentage change due to the impact of coitus. It is estimated that a 25% difference in drug concentration levels due to coitus would be biologically important to be able to detect. Thus, a CV of 1.5 translates to a standard deviation of 37.5%, and with a sample size of 20 couples, this study is designed with 80% power to detect at least a 25% difference in drug concentration levels due to coitus.

Based on a one-sample, paired t-test, the table below summarizes the power available to detect various percentage differences in drug concentration levels due to coitus for a sample size of 20 couples. The table also provides this information for various estimates of the standard deviation (Sigma) in the case that our assumptions are not met.

Table 18: Power for Minimum Detectable Differences in Drug Concentration Levels for Within Group Comparisons of Gel Use vs. Gel Use Prior to Coitus (N=20)

Minimum detectable difference in drug concentration levels	Sigma (CV)				
	0.25 (1.0)	**0.3125 (1.25)**	**0.375 (1.5)**	**0.4375 (1.75)**	**0.5 (2.0)**
5%	0.136	0.104	0.088	0.077	0.071
10%	0.397	0.274	0.205	0.163	0.136
15%	0.721	0.531	0.397	0.308	0.247
20%	0.924	0.775	0.619	0.492	0.397
25%	0.989	0.924	0.807	0.679	0.565
30%	>0.999	0.982	0.924	0.829	0.721
35%	>0.999	0.997	0.977	0.924	0.844
40%	>0.999	>0.999	0.995	0.972	0.924
45%	>0.999	>0.999	>0.999	0.992	0.968
50%	>0.999	>0.999	>0.999	0.998	0.989

10.4.2 Pharmacodynamic Endpoint

In the table below, a power calculation is provided for the pharmacodynamics primary endpoint to assess the impact of coitus (and semen) on PD of luminal drug by measuring the anti-HIV-1 activity in CVL samples.

In the tenofovir 14-day study, the standard deviation of the percent inhibition of HIV-1 activity among participants in the tenofovir arm at Days 3 and 7 was 21.1% and 22.9%, respectively.[25] In comparison, we estimate the standard deviation of the percent inhibition of HIV-1 from the Keller PRO 2000 gel study to be 17.2% for the difference between the post-coital, post-gel visit and the post-gel visit, which is similar to the variability in the tenofovir 14-day study at Days 3 and 7 post-gel.[5] Assuming a standard deviation of 20.0% for the absolute difference in percent inhibition of HIV-1 between the visits where the female participants dose with gel and engage in coitus vs. the visits where female participants dose with gel and do not engage in coitus. In this study, the table below provides estimates of the power available, based on a one-sample, paired t-test, to detect various minimum detectable absolute differences in percent inhibition of HIV-1.

Table 19: Power for Minimum Detectable Absolute Differences in Percent Inhibition of HIV-1

Minimum detectable absolute difference in % inhibition of HIV-1	Power
2	0.071
4	0.136
6	0.247
8	0.397
10	0.565
12	0.721
14	0.844
16	0.924
18	0.968
20	0.989

This study has moderate (56%) power to detect an absolute difference of at least 10% inhibition of HIV-1 between the visits where the female participants dose with gel and engage in coitus vs. the visits where female participants dose with gel and do not engage in coitus.

10.5 Participant Accrual, Follow-up and Retention

The accrual and follow-up period will be 6-12 months. More than 20 couples may be enrolled into each group to reach the target of 20 evaluable couples in each group.

A couple is considered evaluable if ALL of the following have been achieved:

- The primary pharmacokinetic endpoints (tenofovir levels from cervicovaginal lavage (CVL) and vaginal/cervical tissue biopsies) are provided at both the visits where the female participants dose with gel and engage in coitus and the visits where female participants dose with gel and do not engage in coitus, and
- At each Gel/Sex Visit, the couple has completed coitus, and
- In Group 2, gel has been used daily at least 5 of the 7 days prior to the study visits

Couples in Group 1 will be followed for approximately 8 weeks and couples in Group 2 will be followed for approximately 14 weeks.

As stated above in the definition of an evaluable couple, to adequately assess the primary PK objective of this study, it is important for each couple to provide complete data throughout follow-up. Thus, target retention should be set at 100%. Once a couple is enrolled in the study, the study site will make every reasonable effort to retain the couple for the entire study period so that they are evaluable.

10.6 Data Monitoring and Analysis

10.6.1 Study Monitoring Committee

No Data and Safety Monitoring Board oversight is planned for this study. The MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, study or lab issues. These reviews will take place approximately every 4-6 months, and as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

10.6.2 Data 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). Typically, within-group assessment of the difference between time-points will be analyzed using McNemar's test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables).

Primary Pharmacokinetics Analysis

To assess the impact of coitus (and semen) on the pharmacokinetics (PK) of tenofovir 1% gel in female genital tract secretions, vaginal/cervical tissue and rectal tract secretions, the concentration change in tenofovir and tenofovir diphosphate between the visits where the female participants dose with gel and engage in coitus vs. the visits where female participants dose with gel and do not engage in coitus will be assessed for drug concentration levels from vaginal/cervical tissue, blood, and rectal tract secretions within each group (Single Dose/BAT Cohort and Multiple Dose Cohort). The concentration change in tenofovir between these visits will also be assessed for drug concentration levels from CVL. For these analyses, the mean percentage change in drug concentration (DC) due to the impact of coitus will be calculated for each of the following PK assessments:

1. Tenofovir DC in CVL
2. Tenofovir DC on the cervical cytobrush
3. Tenofovir DC in vaginal tissue
4. Tenofovir DC in cervical tissue
5. Tenofovir-diphosphate DC in vaginal tissue
6. Tenofovir-diphosphate DC in cervical tissue
7. Tenofovir DC in blood
8. Tenofovir-diphosphate DC in blood
9. Tenofovir DC from rectal secretions

where the percentage change is defined for each couple as

Percentage change = (1-([Gel/Coitus DC] / [Gel/No Coitus DC]) x 100%

The difference in drug concentration levels at the visits where the female participants dose with gel and engage in coitus vs. the visits where female participants dose with gel and do not engage in coitus will be analyzed using the paired t-test or Wilcoxon signed-ranks test, as appropriate. In Group 1, for assessment of the BAT dosing regimen, DC from the visit were female participants perform BAT dosing with gel, coitus, and post-coitus gel will be compared to DC from the visit where female participants dose with gel (-1 hour) and do not engage in coitus. The BAT DC will also be compared to the visit where female participants dose with gel (-1 hour) and engage in coitus.

For each of the nine (9) assessments, the estimate of the mean percentage change along with the corresponding two-sided p-value and a 95% confidence interval will be presented. Significance level p-values will be adjusted for multiple comparisons using the FDR method.

In addition, change in amount (mass) of vaginal drug after dosing will also be assessed in CVL in similar fashion. As an explanatory variable, the screening semen sample from the male partner will be used to assess the typical semen biomarker value for each male participant so that the volume of ejaculate can be assessed using the CVL.

Primary Pharmacodynamic Analysis

In order to assess the impact of coitus (and semen) on pharmacodynamics (PD) of luminal drug by measuring the anti-HIV-1 activity in CVL samples, antiviral activity (percent inhibition) will be compared at various visits within each cohort. For Group 1, the difference in mean percent inhibition will be compared between:

1. No gel use with coitus vs. endogenous activity (baseline) (impact of coitus on endogenous activity)

For each group, and dose timing (-1 and -24 hours in Group 1 and -1 and -72 hours in Group 2), the difference in mean percent inhibition will be compared between:

2. Gel use alone vs. endogenous activity (baseline) (PD in absence of coitus)
3. Gel use with coitus vs. endogenous activity (baseline) (PD of product following coitus compared to baseline CVL activity)
4. Gel use alone vs. gel use with coitus (Difference in PD in the absence vs following coitus)
5. Gel use with coitus vs. no gel use with coitus (Group 1 only) (PD of product following coitus compared to post-coitus endogenous activity)

In Group 1, for assessment of the BAT dosing regimen, the difference in mean percent inhibition will be compared between:

1. Gel use, coitus, and post-coital gel use vs. endogenous activity (baseline) (PD of BAT compared to baseline CVL activity)
2. Gel use, coitus, and post-coital gel use vs. gel use (-1 hour) alone (Difference in PD of BAT compared to absence of coitus and post-coital gel)
3. Gel use, coitus, and post-coital gel use vs. gel use (-1 hour) with coitus (Difference in PD of BAT compared to absence of post-coital gel)
4. Gel use, coitus, and post-coital gel use vs. no gel use with coitus (PD of BAT compared to post-coitus endogenous activity)

Differences will be assessed with the use of the paired t-test or Wilcoxon signed-ranks test, as appropriate.

Secondary Acceptability Analysis

Descriptive statistics will be used to summarize behavioral, adherence, and acceptability data. Behavioral characteristics will be described in terms of the proportion of couples reporting sexual behaviors and practices prohibited during study participation. The adherence to product use will be described among couples in the Multiple Dose Cohort (Group 2) only, and will include assessment of the number and percentage of expected daily doses taken. The perceived acceptability of study procedures and use of the product will be described by the proportion of couples indicating that the product or procedures where found to be acceptable. The proportion of couples willing to take part in a trial of similar design in the future will be calculated. No formal testing will be performed.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries will be routinely generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents. Data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with current DAIDS policies. (http://rsc.tech-res.com/policiesandregulations/)

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations regarding

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

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

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with current DAIDS policies.(http://rsc.tech-res.com/policiesandregulations/)

12 CLINICAL SITE MONITORING

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

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including CFR Title 45 Part 46 and Title 21 Parts 50, 56, and 312
- Perform source document verification to ensure the accuracy and completeness of study data
- Verify proper collection and storage of biological specimens
- Verify proper storage, dispensing, and accountability of investigational study products
- Assess implementation and documentation of internal site quality management procedures
- The IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, CONRAD, SDMC, NL, NIAID, FDA, OHRP and local and US regulatory authorities, IRBs and study staff

. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

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

13.1 Institutional Review Boards

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

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

13.2 Protocol Registration

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

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

registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

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

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

13.3 Study Coordination

CONRAD holds the Investigational New Drug (IND) application for this study. Copies of all regulatory documents submitted to this IND by CONRAD are forwarded to DAIDS for cross-referencing with other INDs for the study product. Assignment of all sponsor responsibilities for this study will be specified in a Clinical 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 MO. Study implementation will also be guided by a common study-specific procedures manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN CORE, SDMC, NL and other designated members of the Protocol Team.

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

13.4 Risk Benefit Statement

13.4.1 Risks

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

Phlebotomy may lead to excessive bleeding, discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Pelvic examination may cause mild discomfort and/or vaginal bleeding or spotting in the women. 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.

For female participants, vaginal and cervical biopsies carry the risk of discomfort or pain during the procedure and for a few hours afterwards. Participants may have mild vaginal spotting (bleeding) for one or two days, and will be instructed to avoid coitus until bleeding stops. Participants may also be at increased risk for STIs and HIV acquisition, if exposed. Some temporary discomfort with sexual intercourse may occur if the biopsy areas are still healing. There is a small risk of infection and heavier bleeding. If the symptoms are bothersome, if heavy bleeding is noted (soaking through a pad or tampon in an hour or less) or if the participant develops any abnormal odor or discharge from the vagina participants will be instructed to contact the clinic.

During the genital and pelvic examination male and female participants may feel mild pressure, discomfort and/or embarrassment.

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result. For example, in an effort to comply with local requirements to report communicable diseases including HIV-1, sites may be required to report these diseases to local health authorities. Participants also could have problems in their partner relationships associated with use or attempted use of study product.

Tenofovir 1% Gel
Administration of tenofovir gel intravaginally at 0.3% and 1% concentrations in the HPTN 050 Phase1 study resulted in minimal local irritation and little or no systemic AEs were identified. Although 92% of participants reported at least 1 AE, 87% of those reported AEs were mild, and 70% of the AEs were limited to the genitourinary tract. Four severe AEs were reported, with only one, lower abdominal pain, thought to be product-related. The risks associated with tenofovir gel are believed to be less than those identified for systemic use. Some of the possible side effects of the study gel are dryness, itching, burning, or pain in the genital area.

In the HPTN 050 Phase1 study of tenofovir gel, serum PK analysis in a subset of participants demonstrated that there is no clinically significant systemic toxicity. Fourteen of 25 women with PK results had low, but detectable, serum tenofovir levels. Given that Phase 1 data demonstrate measurable plasma concentrations of tenofovir in some participants, participants with hepatitis B infection might be at risk for development of tenofovir-resistant hepatitis B. However, participants with known hepatitis B infection will not be eligible for enrollment. It is not known what effect tenofovir gel could have on the HIV virus or HIV disease progression in HIV-infected participants or their partners. There is a theoretical risk that tenofovir absorbed systemically from oral TDF or vaginal tenofovir gel could result in mutations of the HIV virus in participants who become infected with HIV during the study, or their partner, if the partner is infected with HIV. Limited resistance data from HPTN 050 show no new resistance mutations in plasma or cervicovaginal lavage specimens after 14 days of tenofovir gel use. No participant had high level tenofovir mutations (e.g., K65R).

In a male tolerance study of tenofovir 1% gel, there were few genital findings observed after product use and all findings were classified as mild, small in size and required no treatment.[26] The most common side effects include mild pain (burning, irritation, discomfort) and itching. All reported urogenital symptoms were felt to be mild.

In CAPRISA 004, there were no serious adverse events deemed related to the use of study product. No renal disorders were observed in the study. Mild, self-limiting diarrhea was more common among women who used tenofovir gel (16.9 percent) compared to women who used the placebo gel (11.0 percent). No tenofovir resistance was observed among the women who became infected with HIV in the tenofovir group. No increase in hepatic flares was observed in participants infected with the hepatitis B virus. There were no safety concerns in the 54 pregnancies observed in the trial.

13.4.2 Benefits

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

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

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to both screening and enrollment. Written informed consent also will be obtained for long-term specimen storage and possible future testing, although consent for long-term specimen storage is not required for study participation. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://rsc.tech-res.com/policiesandregulations/). Participants will be provided with a copy of the informed consent form if they are willing to receive it.

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

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

- The unknown safety and unproven efficacy of the study products
- The need to abstain from coitus for a prescribed period of time prior to study visits
- The importance of participants in the study groups to the success of the study
- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The real yet limited benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

13.6 Participant Confidentiality

All study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible, including ensuring participant privacy and confidentiality at the hotel (or equivalent). Each study site will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. For guidance please reference the MTN-011 SSP Manual available at www.mtnstopshiv.org/. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers to identifying information will be stored in a separate, locked file in an area with limited access. 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
- Representatives of CONRAD
- Study staff
- Site IRBs

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

13.7 Special Populations

13.7.1 Pregnant Women

Women who test positive for pregnancy at Screening or Enrollment will not be eligible to participate in this study. Should a woman test positive for pregnancy after Enrollment, a product discontinuation will be implemented and the participant will be terminated from study participation, as per Section 7.6.2. During the informed consent process, women will be informed that study gel is not a method of contraception and the effects of the study gel on a developing human fetus are unknown.

Women who become pregnant during the study period following enrollment and exposure to study product will discontinue product use and be terminated from the study.

13.7.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study meets "Justifications for Exclusion" criteria for younger children as set forth by the NIH. Specifically, "insufficient data are available in adults to judge potential risk

in children" and "children should not be the initial group to be involved in research studies." This study does not plan to enroll children.

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 informed consent forms.

13.9 Communicable Disease Reporting

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

13.10 Access to HIV-related Care

13.10.1 HIV Counseling and Testing

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV-1 screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV-1 testing time-point. Testing will be performed in accordance with the algorithm in Appendix III. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will emphasize the unknown efficacy of the study products in preventing HIV-1 infection. In accordance with the policies of the NIH, participants must receive their HIV-1 test results to take part in this study.

13.10.2 Care for Participants Identified as HIV-Positive

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

<u>Identified as HIV-Positive While on Study Product</u>
Please refer to Section 9.6 for further details. Should a participant test positive for HIV after Enrollment, follow-up procedures will be performed as per Section 7.6.1.

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 CONRAD and NIAID will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS, NIAID, NIMH, and CONRAD for review prior to submission.

15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS: GROUP 1

GROUP 1	Visit 1	Visit 2a	Visit 2b	Visit 3a	Visit 3b	Visit 4a	Visit 4b	Visit 5a	Visit 5b	Visit 6a	Visit 6b	Visit 7a	Visit 7b
	SCR: NO GEL/ NO SEX	ENR: NO GEL/ SEX	Post Coital Samples (♀)	GEL - 1/ SEX	Post Coital Samples (♀)	GEL -1/No Sex (♀)	Samples (♀)	Gel -24/ Sex	Post Coital Samples (♀)	Gel -24/No Sex (♀)	Samples (♀)	Gel - 1/Sex/ Gel +1	Post-Coital Samples/ Final Clinic
Administrative and Regulatory													
Informed consent	X												
Informed consent comprehension assessment	X												
Eligibility assessment	X	X											
Eligibility confirmation		X											
Eligibility to continue study participation, including continued monogamy				X		X		X		X		X	
Assignment of PTID	X												
Locator information	X	X		X		X		X		X		X	
Demographic information	X												
Reimbursement	X	X	X	X	X	X	X	X	X	X	X	X	X
Schedule next visit or contact	*	*	*	*	*	*	*	*	*	*	*	*	*
Provision of coitus visit instructions		X		X				X				X	
Collect coitus visit data (FEMALE ONLY)			X		X				X				X
Clinical													
Medical and/or menstrual history	X	X		X		X		X		X		X	
Concomitant medications	X	X		X		X		X		X		X	
Perform a full/modified physical examination	X	X		X		X		X		X		X	*
Pelvic examination (FEMALE ONLY)	X	X	X	*	X	*	X	*	X	*	X	*	X
Genital examination (MALE ONLY)	X	X		*				*				*	X
Offer panty liners (FEMALE ONLY)		X		X		X		X		X		X	
Disclosure of available test results	X	X		X		X		X		X		X	*
Treat or prescribe treatment for UTI/RTI/STIs or refer	*	*		*		*		*		*		*	*
Record/update AEs			X		X		X		X		X		X
Semen sample (MALE ONLY)	X												
Behavioral/ Counseling													
Conduct behavioral assessment		X			X		X		X		X		X
Conduct acceptability assessment													X
Provide HIV pre-post- test counseling	X												X

GROUP 1	Visit 1	Visit 2a	Visit 2b	Visit 3a	Visit 3b	Visit 4a	Visit 4b	Visit 5a	Visit 5b	Visit 6a	Visit 6b	Visit 7a	Visit 7b
	SCR: NO GEL/ NO SEX	ENR: NO GEL/ SEX	Post Coital Samples (♀)	GEL - 1/ SEX	Post Coital Samples (♀)	GEL -1/No Sex (♀)	Samples (♀)	Gel -24/ Sex	Post Coital Samples (♀)	Gel -24/No Sex (♀)	Samples (♀)	Gel - 1/Sex/ Gel +1	Post-Coital Samples/ Final Clinic
Provide full/modified HIV/STI risk reduction counseling	X	X		X		X		X		X		X	X
Provide contraceptive counseling (FEMALE ONLY)	X	X		X		X		X		X		X	
Laboratory													
hCG (FEMALE ONLY)	X	X		X		X		X		X		X	
Urine culture	*	*		*		*		*		*		*	*
Urine NAAT for GC/CT	X	*		*		*		*		*		*	*
CBC with platelets (FEMALE ONLY)	X												
HIV-1 serology	X												X
PK- blood (FEMALE ONLY)					X		X		X		X		X
Syphilis serology	X												
HBsAg	X												
Plasma archive		X											
CVL for PK, PD, and/or semen biomarker (FEMALE ONLY)	X		X		X		X		X		X		X
Vaginal fluid pH (FEMALE ONLY)	X	X	X	X	X	X	X	X	X	X	X	X	X
Vaginal and cervical biopsies for PK (FEMALE ONLY)					X		X		X		X		X
Cytobrush (FEMALE ONLY)					X		X		X		X		X
Rapid Trichomonas test (FEMALE ONLY)	X	*		*		*		*		*		*	*
KOH wet mount for candidiasis (FEMALE ONLY)	*	*		*		*		*		*		*	*
Wet mount for BV (FEMALE ONLY)	*	*		*		*		*		*		*	*
Cervical specimen for pap smear (FEMALE ONLY)	*												
Rectal sponge for PK (FEMALE ONLY)					X		X		X		X		X
Study Product													
Provision of study product				X		X		X		X		X	
Collect all used applicators/unused study product					X		X		X		X		X
Study product use instructions				X		X		X		X		X	

X required procedure, * if indicated, ♀= Female participants only

Note: At the Final Visit, participants should receive available test results, however if results are not available study staff should make arrangement to disclose those results

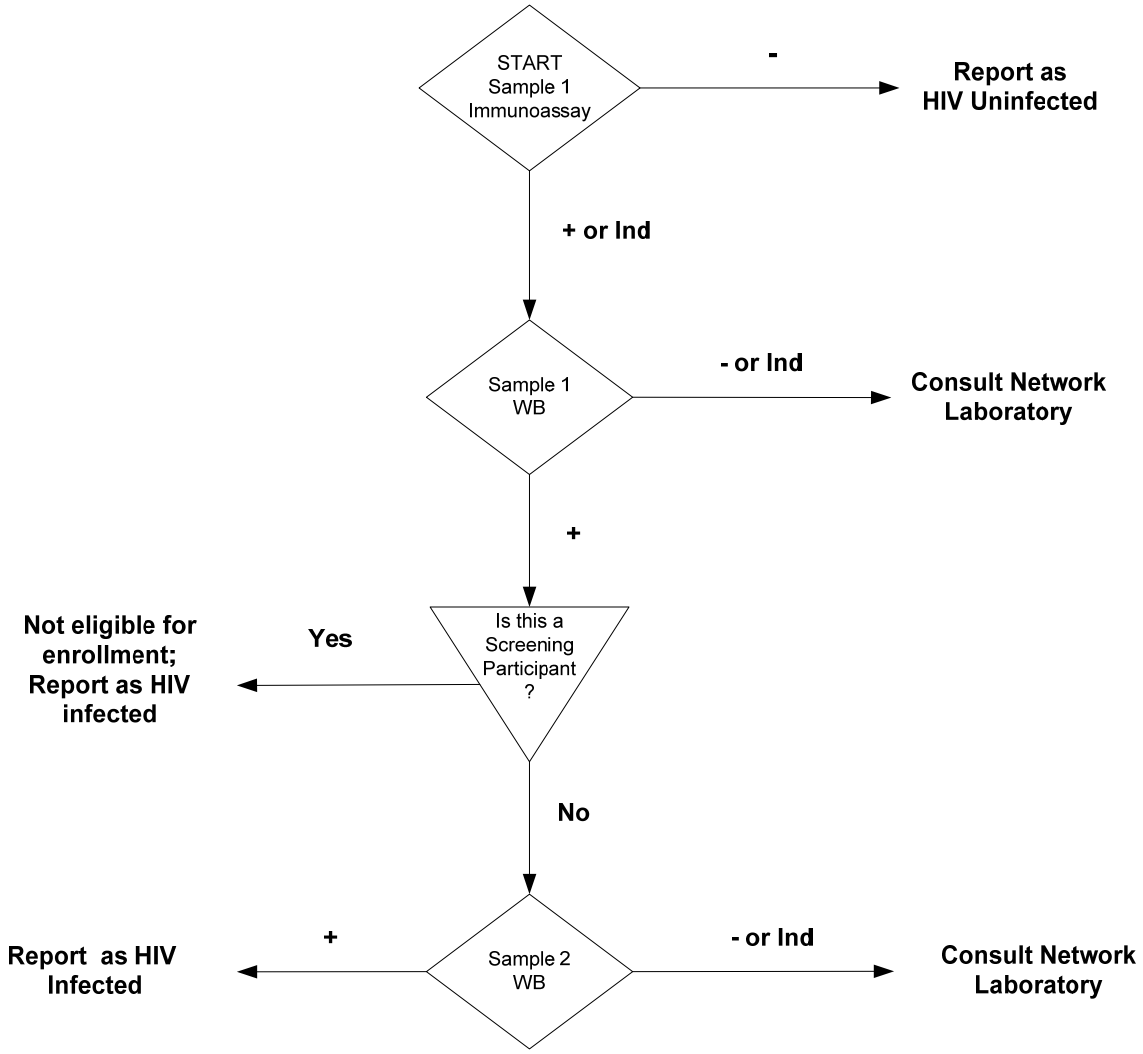
APPENDIX II: SCHEDULE OF STUDY VISITS AND EVALUATIONS: GROUP 2

	Visit 1	Visit 2	Visit 3a	Visit 3b	Visit 4	Visit 5	Visit 6	Visit 7a	Visit 7b	Visit 8	Visit 9
	SCR	ENR	Gel -1/Sex	Post Coital Sampling (♀)	Provision of Product (♀)	Sampling (♀)	Provision of Product (♀)	Gel -72/Sex	Post Coital Sampling (♀)	Provision of Product (♀)	Sampling/ Final Clinic
Administrative and Regulatory											
Informed consent(s)	X										
Informed consent comprehension assessment	X										
Eligibility assessment	X	X									
Eligibility confirmation		X									
Eligibility to continue study participation, including continued monogamy			X		X	X	X	X		X	
Assignment of PTID	X										
Locator information	X	X	X		X	X	X	X		X	
Demographic information	X										
Reimbursement	X	X	X	X	X	X	X	X	X	X	X
Schedule next visit or contact	*	*	*	*	*	*	*	*	*	*	*
Provision of coitus visit instructions			X					X			
Collect coitus visit data (FEMALE ONLY)				X					X		
Clinical											
Medical and/or menstrual history	X	X	X		X	X	X	X		X	X
Concomitant medications	X	X	X		X	X	X	X		X	X
Perform a full/modified physical examination	X	X	X					X			X
Pelvic examination (FEMALE ONLY)	X	X	*	X	*	X	*	*	X	*	X
Genital exam (MALE ONLY)	X	X	*					*			X
Offer panty liners (FEMALE ONLY)		X	X		X		X	X		X	
Disclose available test results	X	X	X		X		X	X		X	*
Treatment or prescribe treatment for UTI/RTI/STIs or refer	*	*	*		*		*	*		*	*
Record/update AEs (FEMALE ONLY)			X	X	X	X	X	X	X	X	X
Record/update AEs (MALE ONLY)											X
Semen sample (MALE ONLY)	X										
Behavioral/Counseling											
Conduct behavioral assessment		X		X		X			X		X
Conduct acceptability assessment											X
Product adherence assessment				X		X			X		
Provide HIV pre-post- test counseling	X										X
Provide full/modified HIV/STI risk reduction counseling	X	X	X		X		X	X		X	X
Provide adherence counseling		X	X		X		X	X		X	

	Visit 1	Visit 2	Visit 3a	Visit 3b	Visit 4	Visit 5	Visit 6	Visit 7a	Visit 7b	Visit 8	Visit 9
	SCR	ENR	Gel -1/Sex	Post Coital Sampling (♀)	Provision of Product (♀)	Sampling (♀)	Provision of Product (♀)	Gel -72/Sex	Post Coital Sampling (♀)	Provision of Product (♀)	Sampling/ Final Clinic
(FEMALE ONLY)											
Provide contraceptive counseling (FEMALE ONLY)	X	X	X		X	X	X	X		X	
Laboratory											
hCG (FEMALE ONLY)	X	X	X		X	X	X	X		X	X
Urine culture	*	*	*		*		*	*		*	*
Urine NAAT for GC/CT	X	*	*		*		*	*		*	*
CBC with platelets (FEMALE ONLY)	X										
HIV-1 serology	X										X
PK- blood (FEMALE ONLY)				X		X			X		X
Syphilis serology	X										
HBsAg	X										
Plasma archive		X									
CVL for PK, PD, and/or semen biomarker (FEMALE ONLY)	X			X		X			X		X
Vaginal fluid pH (FEMALE ONLY)	X	X	X	X	X	X	X	X	X	X	X
Vaginal and cervical biopsies (FEMALE ONLY)				X		X			X		X
Cervical cytobrush (FEMALE ONLY)				X		X			X		X
Rapid Trichomonas test (FEMALE ONLY)	X	*	*		*		*	*		*	*
KOH wet mount for candidiasis (FEMALE ONLY)	*	*	*		*		*	*		*	*
Wet mount for BV (FEMALE ONLY)	*	*	*		*		*	*		*	*
Cervical specimen for pap smear (FEMALE ONLY)	*										
Rectal sponge for PK (FEMALE ONLY)				X		X			X		X
Study Product											
Provision of study product		X	X		X		X	X		X	
Collect all used applicators/unused study product			X	X		X		X	X		X
Study product use instructions		X	X		X		X	X		X	

X required procedure, * if indicated, ♀= Female participants only
Note: At the Final Visit, participants should receive available test results, however if results are not available study staff should make arrangement to disclose those results

APPENDIX III: ALGORITHM FOR HIV ANTIBODY TESTING



Ind: Indeterminate test results

APPENDIX IV: SAMPLE INFORMED CONSENT DOCUMENT GROUP 1 FEMALE SCREENING AND ENROLLMENT

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-011

Phase 1 Evaluation of the Impact of Coitus on the Pharmacokinetics and Pharmacodynamics of Tenofovir 1% Gel Following Pericoital or Daily Gel Dosing

Version 1.0

April 24, 2012

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study: Coital PK/PD of Tenofovir Gel

INFORMED CONSENT

You are being asked to take part in this research study because you are between the ages of 21 and 46 years of age and you have a male partner who is 21 years of age or older. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). Approximately 40 heterosexual monogamous sexually-active couples who are currently not using condoms or any other barriers to prevent pregnancy or sexually transmitted infections will participate in this study. The product being used in this study is tenofovir 1% gel and is supplied by CONRAD. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to join this study, we want you to know about the study.

This is a consent form for screening and enrollment. This consent form provides you with information about the study, including information regarding the exams and tests involved with this study, including interview questions, urine and blood tests, a physical exam and an exam of your vagina as well as information regarding what is expected of you if you are found to meet the study requirements and decide to enroll into MTN-011

The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this form to keep.

YOUR PARTICIPATION IS VOLUNTARY

Before you learn about the study, it is important that you know the following:

- Your participation is voluntary: You do not have to take part in the study if you do not want to. If anyone has threatened you regarding your participation in this study you should notify study staff immediately.
- You may decide not to take part in the study, or to leave the study at any time, without losing your regular medical care.
- As part of this study, you will be asked to engage in penile-vaginal intercourse with your partner at specific visits.
- Both you and your partner must be eligible and agree to complete the study procedures. If any information is learned about you or your partner's health or behavior during the enrollment visit or at any other visit, you may not be able to complete the rest of the scheduled study visits. Information you provide during your participation is confidential. Your test results and other personal information will not be shared with your partner, unless you specifically ask staff to provide your partner with this information, in which case you would need to provide written permission for these tests to be shared.
- If you or your partner decides not to take part in the study, you can still join another study later, if one is available and you qualify. You are asked to tell the study staff about any other studies you are taking part in, or thinking of taking part in.

PURPOSE OF THE STUDY

MTN-011 is testing one product, a gel that is put in the vagina called tenofovir gel. The main purpose of this study is to help researchers:

- Develop a better understanding of the impact of penile-vaginal intercourse on the absorption of tenofovir 1% gel when applied vaginally
- Examine how penile-vaginal intercourse in the presence of tenofovir 1% gel affects the vaginal environment
- Understand whether the gel is acceptable to users

Tenofovir gel is a drug being developed as a microbicide. A microbicide is a drug or agent that is capable of preventing HIV infection. Results from a study testing tenofovir gel, CAPRISA 004, were published in 2010. CAPRISA 004 was done to find out if tenofovir gel could protect women from getting HIV, and to test the gel's safety. The results of CAPRISA 004 showed that women who received tenofovir gel had a lower risk of getting HIV during the trial, compared to women who received placebo gel. Tenofovir gel also showed some protection against new cases of herpes. An additional study called, VOICE, asked women to use tenofovir gel daily. Tenofovir gel did not show a protective effect against HIV in VOICE. MTN-011 will

help us to better understand the difference in results between VOICE and CAPRISA 004.

The United States Food and Drug Administration (US FDA) has been informed of this study and has permitted it to be conducted. [The [local authority] also has permitted the study to be conducted.]

This study will involve two sites in the United States. Including the screening period, you will be enrolled in this study for up to 3 months.

STUDY PRODUCT AND PROCEDURE OVERVIEW

If you decide to take part in the study, your visit will continue today, after you read, discuss, understand, and sign this form. You will discuss with study staff the rules of the study and your understanding of the rules. If you agree to participate and if you and your partner are found to be eligible, you will have a total of 13 visits including the screening visit. Your partner will have a total of 6 visits. Your study visits will take place here and you will be asked to engage in sex with your partner four times at the [sites to insert location].

A summary of the visit schedule is as follows:

Group 1						
Gel	**Visit**	**Visit Name**	**Couple Visit**	**Single Dose of Gel Before Sex/Visit**	**Sex**	**Single Dose of Gel After Sex**
	1	Screening	X			
	2a	Enrollment, No Gel/Sex	X		X	
	2b	Post-Sex Sampling				
-1 hr	3a	Gel -1/Sex	X	X	X	
	3b	Post-Sex Sampling				
	4a	Gel -1/No Sex		X		
	4b	Sampling				
-24 hr	5a	Gel -24/Sex	X	X	X	
	5b	Post-Sex Sampling				
	6a	Gel -24/No Sex		X		
	6b	Sampling				
BAT	7a	Gel -1/Sex/ Gel +1	X	X	X	X
	7b/ Final	Post-Sex Sampling	X			

Approximately 2-3 days after the final day of your period (when you stop bleeding) following Visit 1, Screening Visit, you and your partner will return to the clinic for Visit 2a Enrollment- No Gel/Sex. If you do not have a period other scheduling arrangements will be made. You will be asked to have sex at this visit, but you will

not use study product. Prior to the sex visit, you will receive sex visit instructions, including when you should return to the study clinic (no more than 2 hours after completing sex) and other information about the study, similar instructions will be given to you before each visit involving sex. After the sex act you will return to the clinic for sampling procedures (Visit 2b- Post-Sex Sampling).

Approximately 3-7 days following Visit 2b, you and your partner will return to the clinic (Visit 3a- Gel -1hr/Sex). You will be provided with study gel and instructions, including how to use the study gel and when to apply it (approximately 1 hour prior to sex). You will then engage in sex with your partner and return to the clinic no more than 2 hours after completing the sex act and undergo post-sex sampling procedures (Visit 3b- Post-Sex Sampling).

After a minimum 10-day washout period, you will return to the clinic for Visit 4a (Gel -1hr/ No Sex). At this visit you will apply a single dose of gel and then have sampling procedures at a similar time to that at Visit 3b- Post-Sex Sampling.

After a minimum 10-day washout period, you and your partner will return to the clinic for Visit 5a (Gel -24hr/Sex), you will insert a single dose of gel vaginally 24 hours prior to engaging in sex. You will have sex with your partner and sampling procedures will follow, no more than 2 hours after sex (Visit 5b- Post-Sex Sampling). Following a 10-day minimum washout period, you will return to the clinic for Visit 6a (Gel -24/No Sex). You will apply one applicator of tenofovir 1% gel in the clinic and will return to the clinic approximately 24 hours later for Visit 6b (Sampling).

Following a minimum 10-day washout period, you and your partner will return for Visit 7a (Gel -1/Sex/ Gel +1), you will insert into the vagina the content of one applicator of tenofovir 1% gel approximately 1 hour prior to engaging in sex and you will insert another dose approximately 1 hour after sex. Both doses of the study product will be vaginally inserted at the location where sex is to occur. Sampling procedures will occur approximately 2 hours after sex (Visit 7b/Final Post-Sex Sampling). Your male partner will be asked to attend Visit 7b as well.

WHAT DO I HAVE TO DO IF I TAKE PART IN THE SCREENING EXAMS AND TESTS?

The procedures done during the screening portion of this visit will take about [sites to insert time]. Not all of your results will be available right away. Study staff will inform you of your results when they become available.

- Study staff will ask you where you live and other questions about you, your medical health (including what medications you are taking and your menstrual cycle), your sexual practices and your understanding of the study requirements.

- Study staff will:

- Perform a physical exam

- Talk with you about the requirements of the study and your understanding of the study including, but not limited to:
  - You must agree to engage in penile-vaginal intercourse with your current partner at specific visits at a specified location outside of the clinic, but nearby (hotel or similar location) [INSERT NAME OF HOTEL OR SIMILAR LOCATION] [INSERT CONFIDENTIALITY PROTECTION PROCEDURES.]
  - Agree to abstain from intercourse (oral, anal, or penile-vaginal) and other practices (e.g., masturbation, douching, tampon use, application of lubricants/spermicides or other related practices) 72 hours prior to each follow-up visit
  - Not having a sexually transmitted infection (STI) in the past 6 months
  - Being in a monogamous relationship with your partner for six months and the intention to stay in this relationship for at least another 4 months
  - You must be on an effective form of contraception, other than a contraceptive vaginal ring or intrauterine device (IUD), for 3 months before the Screening and Enrollment visits approved for use in this study, including; oral contraceptive, patch, injectable hormones, subdermal implants, female or male sterilization.

- You will have a pelvic exam, during which time:
  - The study doctor or nurse will use a speculum, a plastic or metal instrument used to separate the walls of the vagina. The study doctor or nurse will check your vagina and cervix for signs of infection, and other problems. They may also take some fluids to test for sexually transmitted infections or diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary.
  - A clinician will rinse your vagina and cervix with about 2 teaspoons of sterile fluid and collect that fluid into a tube for testing. This procedure is called a cervicovaginal lavage (CVL).
  - The study staff may also collect samples from your cervix for a “Pap test” or “Pap smear” if you don’t have results from a Pap test done in the past 12 months. If the test is abnormal, it could mean you have cervical cancer, or that you should have more tests or treatment to lower your chances of having it turn into cervical cancer. It takes about [INSERT AMOUNT OF TIME] before Pap test results are ready. If you have a written report confirming a normal Pap test in the past 12 months or if you had an abnormal Pap test but had follow-up indicating no treatment was required, you will not need to have a Pap test taken at this Screening visit. The results of your Pap test may affect whether or not you can continue in the study.

- Test your urine for:
  - Infections passed through sex
  - Pregnancy

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

- Give you treatment or refer you for treatment for infections passed through sex or other services, if needed.

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

- Schedule your next visit to enroll in MTN-011, if you are willing and eligible

ENROLLMENT and STUDY PROCEDURES

If you and your partner are found to be eligible for this study you may continue to participate in this study. Below you will find a summary of all of the procedures involved with confirming your eligibility and participating in this study.

- Talk with study staff about the following:
  - Your medical health (including whether you have had any medical issues and what medications you are taking) and your menstrual cycle, at all visits
  - Where you live and other questions about you, at all visits except your final clinic visit
  - Your sexual practices and other questions from study staff to ensure that you are still allowed to continue in this study, at all study visits except your final clinic visit
  - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex, except at your final clinic visit
  - Contraception and ways to avoid getting pregnant, at all study visits except your final clinic visit

- The procedures you should follow during your sex visit
- You will also need to provide information about your sex visit, such as when you dosed with gel and when you began having sex

- You will be asked to:
  - Schedule your next visit, when needed (except at your final visit)
  - Answer questions about your experience using the gel and other questions about your sexual practices. Some of these questions may be asked on a computer, the study clinic staff will provide you with instruction prior to using the computer. These questions will be asked following the use of study product and/or after sex, if applicable
  - Bring your used applicators/unused study product (if any) back to the clinic after you have used study product

- The following clinical procedures will be performed:

  - A physical exam will be completed prior at visits when you receive study product and/or before have with your partner.

  - You will be asked to provide blood samples [INSERT AMOUNT] :
    - To be kept frozen and used, only if needed to check on your health or if there are questions about your lab tests, at Visit 2 only
    - To test for infections passed through sex, including HIV at your final visit
      - It is important that you know that you will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we know your status for sure. We will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.
    - Provide blood samples to see how much of the study product is being absorbed by your body and how it affects your body. This will be collected at visits after you used study product and had sex, if applicable

  - Provide a urine sample to see if you are pregnant at all study visits

  - You will have a pelvic exam following the use of study product and sex, if applicable. The study doctor or nurse will use a speculum, a plastic or metal instrument used to separate the walls of the vagina. At visits

when you have sexual intercourse, the pelvic exam will occur approximately two hours after sex. The study doctor or nurse will check your vagina and cervix for signs of infection, and other problems.

- They may also take some fluids to test for sexually transmitted infections or diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary.
- Clinicians will collect fluid from your vagina to see if semen is present after you have engaged in sex
- Also during these pelvic exams, a clinician will perform a cervicovaginal lavage (CVL). This will help study physicians understand how much of the study product is being absorbed by your body and how it affects your body. This will be collected following the use of study product and sex, if applicable
- You will be asked to give tissue samples (biopsies) from your vagina and cervix. A study clinician will collect this biopsy using a special medical tool specifically designed to collect these samples. Approximately 2 samples will be collected, each about 3 mm by 5 mm around, or as big as a grain of rice. These will be collected at visits following the use of study product and sex, if applicable. Like the CVL, your biopsies will help study physicians understand how much of the study product is being absorbed by your body and how it affects your body.
- You will be asked to allow the study clinician to collect cells from your cervix using a brush, at visits following the use of study product and sex, if applicable. These cells will help clinicians understand how much of the study drug was absorbed.
- Finally, you will be asked to provide a rectal sponge sample at visits following the use of study product and sex, if applicable. The rectal sponge sample will be collected by a clinician who will insert a sponge into your rectum to collect fluid. Like the CVL, biopsies, and cervical brush samples; rectal sponges will help study physicians understand how much of the study product is being absorbed by your body and how it affects your body.

As part of having clinical procedures performed, you will:

- Receive treatment or be referred for treatment for problems that the study staff may find
- Receive available test results from study staff

You will be asked to use the study product. This will also require you to use the study product at the location where you have sex. As part of using the study product, you will be asked to do the following:

- Receive applicators containing gel.
- Receive instructions on how to use the gel.

You will also be offered panty liners.

For your safety, it is important that you only use the gel in your vagina, as instructed by study staff.

Finally, you and your partner will be asked to engage in intercourse on four occasions.

AT ANY TIME IN THE STUDY

If you have health problems or if there's any problem interpreting your laboratory tests or if there's any concern regarding your health you may need to:

- Have an exam of your genital area and inside your vagina.
- Give blood, urine, and/or vaginal fluid to test for infections passed through sex. Some fluids also will be collected by swab to test for factors that could affect the chances of getting HIV.
- Get treatment for most types of infections if you need it.

In the unlikely event that you become infected with HIV.
As described above, if you are thought to have HIV, you will have at least three HIV tests to confirm your results. You will be asked to give additional blood (XX mL) for tests to examine the amount of HIV in your blood and whether any HIV in your blood is resistant to medications used to treat HIV. Results of the resistance tests will be provided if these are needed for your medical care.

If the HIV tests confirm that you or your partner have been infected with HIV, you will stop using gel, and your participation in the study will end.

Study staff will give you counseling and referrals for medical care and other services available to you. With your written permission, study staff may share information including test results that may be helpful to your health care provider.

RISKS AND/OR DISCOMFORTS

Whenever your blood is drawn, you may:

- Feel discomfort or pain when your blood is drawn
- Feel dizzy or faint, but most people do not have this reaction
- Have more than expected bleeding, a bruise, swelling, small clot, or infection where the needle goes in your arm or finger

When women have pelvic exams:

- Feel discomfort in your genital area and inside your vagina

- Have a small amount of vaginal bleeding which will stop shortly after the exam

Vaginal/Cervical biopsies:

- When you have vaginal and cervical biopsies you may experience discomfort or pain during the procedure and for a few hours afterwards. You may have mild vaginal spotting (bleeding) for one or two days, and will be instructed to avoid sex until bleeding stops. You may also be at increased risk for STIs and HIV acquisition, if exposed. Some temporary discomfort with sexual intercourse may occur if the biopsy areas are still healing. There is a small risk of infection and heavier bleeding. If the symptoms are bothersome, if heavy bleeding is noted (soaking through a pad or tampon in an hour or less) or if you develop any abnormal odor or discharge from the vagina you should contact the clinic.

When you answer computer questions:

- There are few risks to you from answering the computer questions. Your answers to the questions will be stored on a larger computer here at [INSERT STUDY SITE] that can only be accessed by authorized study staff. Your answers then will be transferred to the same place where your study forms are sent. As with all of your study information, every effort will be made to keep your personal information confidential. Your answers will be identified by your study number only (not your name). However, absolute confidentiality cannot be guaranteed.

The gel could cause some effects. We do not yet know all the effects of the gel. Some, but not all, women who used the gels in other studies have had:

- Dryness, itching, burning feeling, or pain in the genital area
- Vaginal candidiasis (a yeast infection)
- Discharge from the vagina
- Irritation in the genital area
- Diarrhea

You could have these effects or other effects that we do not know about.

A small amount of tenofovir may pass from the gel in your vagina into your tissue and blood.

If you become infected with HIV while using gel, it is possible that the medications in the anti-HIV medication, Truvada (which contains the study drug tenofovir and a different drug not used in this study, emtricitabine) would not work against the HIV in your body. If this happened, it could limit your options for HIV treatment. It is for this reason that you must stop using gel if you become infected with HIV. Study

doctors are available to discuss this with you. They can also do blood tests that will show which HIV medications might work best for you.

Other Possible Risks:
We do not know if there are other risks if you use herbal treatments or supplements while you are using gel. Please tell study staff if you are using any herbal treatments or supplements.

You may become worried while waiting for your test results. 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. If you have HIV or other infections, knowing this could make you worried. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality while you are having the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your STI and HIV status could also cause problems between you and your partner. Also, if your partner finds out that you have not been monogamous, this may cause problems in your relationship. Study Staff will not disclose any information that you tell them to your partner, but it is possible that your partner may find out.

If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them if you would like.

Pregnancy and Breastfeeding
Tenofovir is not birth control. We do not know if tenofovir gel has any effect on pregnancy, the fetuses of women who use the gels when pregnant, or the babies of women who use the gels when breastfeeding. Because of this, pregnant women and women who are breastfeeding must not join this study. Women who join the study must use effective contraception and have pregnancy tests while in the study. Effective contraception includes hormonal methods (oral contraceptive, patch, injectable hormones, subdermal implants) and sterilization of you or your partner. You should not use spermicides as a method of contraception while participating in MTN-011.

If you become pregnant during the study, the study staff will refer you to available sources of medical care and other services you or your baby may need. The study does not pay for this care. You will stop using the gel and will discontinue your participation in this study. The study staff will need to contact you to obtain information about the outcome of your pregnancy.

BENEFITS

You may get no direct benefit from being in this study.

You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV prevention. This is true no matter what study group you are in.

You will have physical exams and genital exams. You will have tests to check on the health of your blood. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you. [*For selected sites only:* If your Pap test result is abnormal, you will be referred for treatment at the [SITES TO INSERT NAME OF PROVIDER/CENTER].]

You and your partner will get counseling and testing for HIV. If you or your partners have infections passed through sex, other than HIV infection, you will be offered or referred to a place where you can get medicine to treat them, if needed. This study does not provide medication for treatment of HIV/AIDS. If you become infected with HIV, you will be referred for medical care, counseling, and other services available to you.

There may be no direct benefits to you from answering the computer questions. However, information learned about the computer questions may help researchers improve the way they collect information about individuals' sexual behaviors.

NEW INFORMATION

You will be told any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the gel may be causing bad effects, or that clearly shows that the gel is very effective in protecting against HIV, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You and your partner may be withdrawn from the study without your consent if either of you:

- become pregnant
- report having sexual intercourse with another person
- are not willing to find out your HIV test results
- become infected with an infection passed through sex
- are not able to attend clinic visits or complete the study procedures
- are taking certain medications
- are taking medication for possible recent exposure to HIV infection

- are unable or unwilling to follow study procedures or instructions
- could be harmed by continuing to take gel

Or if:

- the study is stopped or canceled
- the study staff feels that staying in the study would be harmful to you
- other reasons, decided by the study staff

It is important for you to know that if, at any time your partner is withdrawn from the study your participation in this study will also end.

If you or your partner withdraws early from the study, we will ask you to come in for an early termination visit, all of the procedures planned for the final clinic visit will take place at this time.

ALTERNATIVES TO PARTICIPATION

There are no gels known to protect against HIV during sex. The only known way to protect against HIV during sex is to use a condom every time you have sex.

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

COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you and/or your partner for infections passed through sex other than HIV will be provided free of charge by the study.

REIMBURSEMENT

- [INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT.]

You will receive [$xx] for your time, effort, and travel to and from the clinic at each scheduled visit.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff will use your personal information, if needed, to verify that you are not taking part in any other research studies. This includes other studies conducted by [INSERT SITE NAME] and studies conducted by other researchers

that study staff know about. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [Insert name of applicable Institutional Review Board (IRB), an IRB is a committee that watches over the safety and rights of research participants]
- study staff
- study monitors
- the organization that supplies tenofovir gel (CONRAD)

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

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

STORAGE AND FUTURE TESTING OF SPECIMENS

There might be a small amount of blood, vaginal and cervical fluids and/or tissue left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your leftover blood, vaginal and cervical fluids and/or tissue for testing in future studies. You can still enroll in this study if you decide not to have blood, vaginal and cervical fluids and/or tissue stored for future studies. If you do not want blood, vaginal and cervical fluids and/or tissue stored, we will destroy the left over specimens. Any future studies that may be done will also have to be approved by an IRB.

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

Initial and date

_____ I **do not** agree to allow my biological specimens to be stored and health data to be used in future research studies.

Initial and date

RESEARCH-RELATED INJURY

[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 get additional treatment for your injuries. There is no program to pay money or give other forms of compensation either through this institution or the US National Institutes of Health (NIH) for research-related complications or injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

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

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB or other organization appropriate for the site] at [insert physical address and telephone number]. If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or Community Advisory Board (CAB) member [staff will decide which] at [insert physical address and telephone number].

SIGNATURES

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

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

APPENDIX V: SAMPLE INFORMED CONSENT DOCUMENT GROUP 2 FEMALE SCREENING AND ENROLLMENT

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-011

Phase 1 Evaluation of the Impact of Coitus on the Pharmacokinetics and Pharmacodynamics of Tenofovir 1% Gel Following Pericoital or Daily Gel Dosing

Version 1.0

April 24, 2012

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study: Coital PK/PD of Tenofovir Gel

INFORMED CONSENT

You are being asked to take part in this research study because you are between the ages of 21 and 46 years and you have a male partner who is 21 years of age or older. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). Approximately 40 heterosexual monogamous sexually-active couples who are currently not using condoms or any other barriers to prevent pregnancy or sexually transmitted infections will participate in this study. The product being used in this study is tenofovir 1% gel and is supplied by CONRAD. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to join this study, we want you to know about the study.

This is a consent form for screening and enrollment. This consent form provides you with information about the study, including information regarding the exams and tests involved with this study, including interview questions, urine, and blood tests, a physical exam and an exam of your vagina as well as information regarding what is expected of you if you are found to meet the study requirements and decide to enroll.

The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this form to keep.

YOUR PARTICIPATION IS VOLUNTARY

Before you learn about the study, it is important that you know the following:

- Your participation is voluntary: You do not have to take part in the study if you do not want to. If anyone has threatened you regarding your participation in this study you should notify study staff immediately.
- You may decide not to take part in the study, or to leave the study at any time, without losing your regular medical care.
- As part of this study, you will be asked to engage in penile-vaginal intercourse with your partner at a specific visit.
- Both you and your partner must be eligible and agree to complete the study procedures. If any information is learned about you or your partner's health or behavior during enrollment or at any other visit, you may not be able to complete the rest of the scheduled study visits. Information you provide during your participation is confidential. Your test results and other personal information will not be shared with your partner, unless you specifically ask staff to provide your partner with this information, in which case you would need to provide written permission for these results to be shared.
- If you or your partner decides not to take part in the study, you can still join another study later, if one is available and you qualify. You are asked to tell the study staff about any other studies you are taking part in, or thinking of taking part in.

PURPOSE OF THE STUDY

MTN-011 is testing one product, a gel that is put in the vagina called tenofovir gel. The main purpose of this study is to help researchers:

- Develop a better understanding of the impact of penile-vaginal intercourse on the absorption of tenofovir 1% gel when applied vaginally
- Examine how penile-vaginal intercourse in the presence of tenofovir 1% gel affects the vaginal environment
- Understand whether the gel is acceptable to users

Tenofovir gel is a drug being developed as a microbicide. A microbicide is a drug or agent that is capable of preventing HIV infection. Results from a study testing tenofovir gel, CAPRISA 004, were published in 2010. CAPRISA 004 was done to find out if tenofovir gel could protect women from getting HIV, and to test the gel's safety. The results of CAPRISA 004 showed that women who received tenofovir gel had a lower risk of getting HIV during the trial, compared to women who received placebo gel. Tenofovir gel also showed some protection against new cases of herpes. An additional study called, VOICE, asked women to use tenofovir gel daily. Tenofovir gel did not show a protective effect against HIV in VOICE. MTN-011 will help us to better understand the difference in results between VOICE and CAPRISA 004.

The United States Food and Drug Administration (US FDA) has been informed of this study and has permitted it to be conducted. [The [local authority] also has permitted the study to be conducted.]

This study will involve two sites in the United States. Including the screening period, you will be enrolled in this study for approximately 41/2 months.

STUDY PRODUCT AND PROCEDURE OVERVIEW

If you decide to take part in the study, your visit will continue today, after you read, discuss, understand, and sign this form. You will discuss with study staff the rules of the study and your understanding of the rules. If you agree to participate and if you and your partner are found to be eligible, you will have a total of 11 visits including the screening visit. Your partner will have a total of 5 visits. Your study visits will take place here and you will be asked to engage in sex with your partner at the [sites to insert location].

Group 2					
Gel	**Visit**	**Visit Name**	**Couple Visit**	**7 Daily Doses to be to be Used Before Sex/Visit**	**Sex**
	1	Screening	X		
	2	Enrollment- Provision of Study Product	X	X	
-1 hr	3a	Gel/Sex	X		X
	3b	Post-Sex Sampling			
	4	Provision of Study Product		X	
	5	Sampling			
-72 hr	6	Provision of Study Product		X	X
	7a	Gel/Sex	X		
	7b	Post-Sex Sampling			
	8	Provision of Study Product		X	
	9/ Final	Sampling	X		

Approximately 2-3 days after the final day of the your period (when you stop bleeding) following the Visit 1, Screening Visit, you and your partner will return to the clinic for Visit 2 (Enrollment/Provision of Product). If you do not have a period other scheduling arrangements will be made. You will apply the first dose of gel vaginally and receive enough product to allow you to dose at home for 5 days (doses 2-6) at this visit.

At Visit 3a (Gel -1/Sex), following 6 days of using the product, you and your partner will return to the clinic at which time the 7th dose of product will be provided and

applied by you at the location where sex is to occur (hotel or comparable site). Prior to the sex visit, you will receive sex visit instructions, these instructions will include information regarding when you should insert the study product (approximately 1 hour prior to sex), when you should return to the study clinic (no more than 2 hours after completing sex), and other information about the study. Similar instructions will be given to you before each visit involving sex. You will then engage in sex and return to the clinic to undergo post-sex sampling procedures at Visit 3b (Post-Sex Sampling).

After a minimum 20 day washout period you will return to the clinic, for Visit 4. At Visit 4 (Provision of Study Product), you will apply the first of the 7 daily doses of gel at the clinic and receive enough study product to allow you to insert the gel at home for the next 5 days (doses 2-6).

At Visit 5 (Sampling), you will return to the clinic to insert the 7th dose at the clinic and to undergo sampling procedures.

After a minimum 20 day washout period, you will return for Visit 6 (Provision of Study Product), and will apply the first of 7 daily doses of gel at the clinic and receive enough study product to dose at home for 6 days (doses 2-7).

At Visit 7a (Gel -72/Sex), following 7-days of product use, you and your partner will return to the clinic to engage in sex approximately 72 hours after you inserted your last dose. After the sex act you will return to the clinic to undergo post-sex sampling procedures at Visit 7b (Post-Sex Sampling).

After a minimum 20 day washout period, you will return to the clinic for Visit 8 (Provision of Study Product), you will apply the first of 7 daily doses of gel at the clinic and receive enough study product to allow you to dose for 6 days at home (doses 2-7).

At Visit 9 (Sampling), you and your partner will return to the clinic after you applied the 7th dose of study product approximately 72 hours prior to the visit. You will undergo sampling procedures for the final time and your partner will also have a few procedures.

If you and your partner are found to be eligible for this study you may continue to participate in this study. You will discuss with study staff the rules of the study and your understanding of the rules.

WHAT DO I HAVE TO DO IF I TAKE PART IN THE SCREENING EXAMS AND TESTS?

The procedures done during the screening portion of this visit will take about [sites to insert time]. Not all of your results will be available right away. Study staff will inform you of your results when they become available.

- Study staff will ask you where you live and other questions about you, your medical health (including what medications you are taking and your menstrual cycle), your sexual practices and your understanding of the study requirements.

- Study staff will:

  - Perform a physical exam

  - Talk with you about the requirements of the study and your understanding of the study including, but not limited to:
    - You must agree to engage in penile-vaginal intercourse with your current partner at specific visits at a specified location outside of the clinic, but nearby (hotel or similar location) [INSERT NAME OF HOTEL OR SIMILAR LOCATION] [INSERT CONFIDENTIALITY PROTECTION PROCEDURES.]
    - Agree to abstain from intercourse (oral, anal, or penile-vaginal) and other practices (e.g., masturbation, douching, tampon use, application of lubricants/spermicides or other related practices) 72 hours prior to each follow-up visit and during home gel use
    - Not having a sexually transmitted infection (STI) in the past 6 months
    - Being in a monogamous relationship with your partner for six months and the intention to stay in this relationship for at least another 4 months
    - You must be on an effective form of contraception, other than a contraceptive vaginal ring or intrauterine device (IUD), for 3 months before the Screening and Enrollment visits for use in this study, including; oral contraceptive, patch, injectable hormones, subdermal implants, female or male sterilization.

  - You will have a pelvic exam, during which time:
    - The study doctor or nurse will use a speculum, a plastic or metal instrument used to separate the walls of the vagina. The study doctor or nurse will check your vagina and cervix for signs of infection, and other problems. They may also take some fluids to test for sexually transmitted infections or diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary.
    - A clinician will rinse your vagina and cervix with about 2 teaspoons of sterile fluid and collect that fluid into a tube for testing. This procedure is called a cervicovaginal lavage (CVL).
    - The study staff may also collect samples from your cervix for a “Pap test” or “Pap smear” if you don’t have results from a Pap test done in the past 12 months. If the test is abnormal, it could mean you have cervical cancer, or that you should have more tests or treatment to lower your chances of having it turn into cervical cancer. It takes about

[Sites to insert amount of time] before Pap test results are ready. If you have a written report confirming a normal Pap test in the past 12 months or if you had an abnormal Pap test but had follow-up indicating no treatment was required, you will not need to have a Pap test taken at this Screening visit. The results of your Pap test may affect whether or not you can continue in the study.

- Test your urine for:
  - Infections passed through sex
  - Pregnancy

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

- Give you treatment or refer you for treatment for infections passed through sex or other services, if needed.

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

- Schedule your next visit to enroll in MTN-011, if you are willing and eligible

ENROLLMENT and STUDY PROCEDURES

If you and your partner are found to be eligible for this study you may continue to participate in this study. Below you will find a summary of all of the procedures involved with confirming eligibility and participating in this study.

- Talk with study staff about the following:
  - Your medical health (including whether you have had any medical issues and what medications you are taking) and your menstrual cycle, at all visits, at most visits (these questions will not be asked at your post-sex sampling visits)

- Where you live and other questions about you, at most visits (these questions will not be asked at your post-sex sampling visits or at your final clinic visit)
- Your sexual practices and other questions from study staff to ensure that you are still allowed to continue in this study. These questions will be asked at most visits, but will not be asked at your post-sex sampling visits or at your final clinic visit
- Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex. This will not be completed at visits where sampling occurs
- Contraception and ways to avoid getting pregnant. This will occur at most visits, but will not be performed at your post-sex sampling visits or at your final clinic visit
- How to properly use the study product of the study, if needed
- The procedures that you should follow during and after your sex visit.

- You will be asked to:
  - Receive reminder phone calls or SMS (text messages) to remind you to use your product during your study product use periods.
  - Schedule your next visit, when needed (except at your final visit)
  - Answer questions about your experience using the gel and/or other questions about your sexual practices. Some of these questions may be asked on a computer, the study clinic staff will provide you with instruction prior to using the computer. Questions will be asked at your Enrollment Visit and at visits following the use of study product and sex, if applicable

- The following clinical procedures will be performed:

  - A physical exam will be completed when you enroll in the study and before you engage in sex with your partner and at your final clinic visit.

  - You will be asked to provide blood samples [Sites to insert amount]:
    - To be kept frozen and used, only if needed to check on your health or if there are questions about your lab tests at Visit 2 only
    - To test for infections passed through sex, including HIV at your Final Clinic Visit
      - It is important that you know that you will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we know your status for sure. We will refer you to available sources of medical

care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.

- Provide blood samples to see how much of the study product is being absorbed by your body and how it affects your body. This will be collected at visits following the use of study product and/or sex, if applicable

- Provide a urine sample to see if you are pregnant at most study visits. You will not have a pregnancy test at post-sex sampling visits.

- You will have a pelvic exam following the use of study product and sex, if applicable. The study doctor or nurse will use a speculum, a plastic or metal instrument used to separate the walls of the vagina. At the visit you are asked to have sexual intercourse with your partner, the pelvic exam will occur approximately two hours after sex. The study doctor or nurse will check your vagina and cervix for signs of infection, and other problems.
  - They may also take some fluids to test for sexually transmitted infections or diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary.
  - You will provide vaginal and cervical fluid by cervical vaginal lavage (CVL). This will be collected at visits following the use of study product and sex, if applicable
  - You will be asked to give tissue samples (biopsies) from your vagina and cervix. A study clinician will collect this biopsy using a special medical tool specifically designed to collect these samples. Approximately 2 samples will be collected, each about 3 mm by 5 mm around, or as big as a grain of rice. This will be collected at visits after you used study product (and had sex, if applicable). Like the CVL, your biopsy will help study physicians understand how much of the study product is being absorbed by your body and how it affects your body.
  - You will be asked to allow the study clinician to collect cells from your cervix using a brush, at visits where you used study product and had sex, if applicable. These cells will help clinicians understand how much of the study drug was absorbed.
  - Finally, you will be asked to provide a rectal sponge sample at visits following the use of study product and sex, if applicable. The rectal sponge sample will be collected by a clinician who will insert a sponge into your rectum to collect fluid. Like the CVL and biopsies, and cervical brush samples; rectal sponges will help study physicians understand how much of the study product is being absorbed by your body and how it affects your body.

As part of having clinical procedures performed, you will:

- Receive treatment or be referred for treatment for problems that the study staff may find.
- Receive available test results from study staff

You will be asked to use the study product for seven days each time. As part of using the study product you will be asked to do the following:

- Receive applicators containing gel.
- Receive instructions on how to use the gel. For your safety, it is important that you only use the gel in your vagina, as instructed by study staff.
- Be asked to insert the gel in your vagina once a day, at the same time every day.
- Be asked to bring all applicators (used and unused) back to the clinic.

You will also be offered panty liners.

Finally, you and your partner will be asked to engage in intercourse on two occasions.

AT ANY TIME IN THE STUDY

If you have health problems or if there's any problem interpreting your laboratory tests or if there's any concern regarding your health you may need to:

- Have an exam of your genital area and inside your vagina.
- Give blood, urine, and/or vaginal fluid to test for infections passed through sex. Some fluids also will be collected by swab to test for factors that could affect the chances of getting HIV.
- Get treatment for most types of infections if you need it.

In the unlikely event that you become infected with HIV.
As described above, if you are thought to have HIV, you will have at least three HIV tests to confirm your results. You will be asked to give additional blood (XX mL) for tests to examine the amount of HIV in your blood and whether any HIV in your blood is resistant to medications used to treat HIV. Results of the resistance tests will be provided if these are needed for your medical care. In addition, study staff will ask that you return any study product still in your possession.

If the HIV tests confirm that you or your partner are infected with HIV, you will stop using gel, and your participation in the study will end.

Study staff will give you counseling and referrals for medical care and other services available to you. With your written permission, study staff may share information including test results that may be helpful to your health care provider.

RISKS AND/OR DISCOMFORTS

Whenever your blood is drawn, you may:

- Feel discomfort or pain when your blood is drawn
- Feel dizzy or faint, but most people do not have this reaction.
- Have more than expected bleeding, a bruise, swelling, small clot, or infection where the needle goes in your arm or finger

When women have pelvic exams:

- Feel discomfort in your genital area and inside your vagina.
- Have a small amount of vaginal bleeding which will stop shortly after the exam

Vaginal/Cervical biopsies:

- When you have vaginal and cervical biopsies you may experience discomfort or pain during the procedure and for a few hours afterwards. You may have mild vaginal spotting (bleeding) for one or two days, and will be instructed to avoid sex until bleeding stops. You may also be at increased risk for STIs and HIV acquisition, if exposed. Some temporary discomfort with sexual intercourse may occur if the biopsy areas are still healing. There is a small risk of infection and heavier bleeding. If the symptoms are bothersome, if heavy bleeding is noted (soaking through a pad or tampon in an hour or less) or if you develop any abnormal odor or discharge from the vagina you should contact the clinic.

When you answer computer questions:

- There are few risks to you from answering the computer questions. Your answers to the questions will be stored on a larger computer here at [study site] that can only be accessed by authorized study staff. Your answers then will be transferred to the same place where your study forms are sent. As with all of your study information, every effort will be made to keep your personal information confidential. Your answers will be identified by your study number only (not your name). However, absolute confidentiality cannot be guaranteed.

The gel could cause some effects. We do not yet know all the effects of the gel. Some, but not all, women who used the gels in other studies have had:

- Dryness, itching, burning feeling, or pain in the genital area
- Vaginal candidiasis (a yeast infection)
- Discharge from the vagina
- Irritation in the genital area
- Diarrhea

You could have these effects or other effects that we do not know about.

A small amount of tenofovir may pass from the gel in your vagina into your tissue and blood.

If you become infected with HIV while using gel, it is possible that the medications in the anti-HIV medication, Truvada (which contains the study drug tenofovir and a different drug not used in this study, emtricitabine) would not work against the HIV in your body. If this happened, it could limit your options for HIV treatment. It is for this reason that you must stop using gel if you become infected with HIV. Study doctors are available to discuss this with you. They can also do blood tests that will show which HIV medications might work best for you.

Other Possible Risks:
We do not know if there are other risks if you use herbal treatments or supplements while you are using gel. Please tell study staff if you are using any herbal treatments or supplements.

You may become worried while waiting for your test results. 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. If you have HIV or other infections, knowing this could make you worried. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality while you are having the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your STI and HIV status could also cause problems between you and your partner. Also, if your partner finds out that you have not been monogamous, this may cause problems in your relationship. Study Staff will not disclose any information that you tell them to your partner, but it is possible that your partner may find out.

If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them if you would like.

Pregnancy and Breastfeeding
Tenofovir is not birth control. We do not know if tenofovir gel has any effect on pregnancy, the fetuses of women who use the gels when pregnant, or the babies of women who use the gels when breastfeeding. Because of this, pregnant women and women who are breastfeeding must not join this study. Women who join the study must use effective contraception and have pregnancy tests while in the study. Effective contraception includes hormonal methods (oral contraceptive, patch, injectable hormones, subdermal implants), and sterilization of you or your partner.

You should not use spermicides as a method of contraception while participating in MTN-011.

If you become pregnant during the study, the study staff will refer you to available sources of medical care and other services you or your baby may need. The study does not pay for this care. You will be instructed to stop using the gel and return any study product still in your possession to the clinic. Your participation in this study will be discontinued. The study staff will need to contact you to obtain information about the outcome of your pregnancy.

BENEFITS

You may get no direct benefit from being in this study.

You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV prevention. This is true no matter what study group you are in.

You will have physical exams and genital exams. You will have tests to check on the health of your blood. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you. [*For selected sites only:* If your Pap test result is abnormal, you will be referred for treatment at the [insert name of provider/center].]

You and your partner will get counseling and testing for HIV. If you or your partner have infections passed through sex, other than HIV infection, you will be offered or referred to a place where you can get medicine to treat them, if needed. This study does not provide medication for treatment of HIV/AIDS. If you become infected with HIV, you will be referred for medical care, counseling, and other services available to you.

There may be no direct benefits to you from answering the computer questions. However, information learned about the computer questions may help researchers improve the way they collect information about individuals' sexual behaviors.

NEW INFORMATION

You will be told any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the gel may be causing bad effects, or that clearly shows that the gel is very effective in protecting against HIV, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You and your partner may be withdrawn from the study without your consent if either of you:

- become pregnant.
- report having sexual intercourse with another person
- are not willing to find out your HIV test results.
- become infected with an infection passed through sex
- are not able to attend clinic visits or complete the study procedures.
- are taking certain medications
- are taking medication for possible recent exposure to HIV infection.
- are unable or unwilling to follow study procedures or instructions.
- could be harmed by continuing to take gel.

Or if:

- the study is stopped or canceled.
- the study staff feels that staying in the study would be harmful to you.
- other reasons, decided by the study staff.

It is important for you to know that if, at any time your partner is withdrawn from the study your participation in this study will also end.

If you or your partner withdraws early from the study, we will ask you to come in for an early termination visit, all of the procedures planned for the final clinic visit will take place at this time.

ALTERNATIVES TO PARTICIPATION

There are no gels known to protect against HIV during sex. The only known way to protect against HIV during sex is to use a condom every time you have sex.

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

COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you and/or your partner for infections passed through sex other than HIV will be provided free of charge by the study.

REIMBURSEMENT

- [INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT.]

You will receive [$xx] for your time, effort, and travel to and from the clinic at each scheduled visit.

CONFIDENTIALITY

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

Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert name of applicable Institutional Review Board (IRB), an IRB is a committee that watches over the safety and rights of research participants]
- study staff
- study monitors
- the organization that supplies tenofovir gel (CONRAD)

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

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

STORAGE AND FUTURE TESTING OF SPECIMENS

There might be a small amount of blood, vaginal and cervical fluids and/or tissue left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your leftover blood, vaginal and cervical fluids and/or tissue for testing in future studies. You can still enroll in this study if you decide not to have blood, vaginal and cervical fluids and/or tissue stored for future studies. If you do not want blood, vaginal and cervical fluids and/or tissue stored, we will destroy the left over specimens. Any future studies that may be done will also have to be approved by an IRB.

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

Initial and date

_____ I **do not** agree to allow my biological specimens to be stored and health data to be used in future research studies.

Initial and date

RESEARCH-RELATED INJURY

[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 get additional treatment for your injuries. There is no program to pay money or give other forms of compensation either through this institution or the US National Institutes of Health (NIH) for research-related complications or injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

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

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB or other organization appropriate for the site] at [insert physical address and telephone number]. If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or Community Advisory Board (CAB) member [staff will decide which] at [insert physical address and telephone number].

SIGNATURES

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

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

APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT GROUP 1 MALE SCREENING and ENROLLMENT

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-011

Phase 1 Evaluation of the Impact of Coitus on the Pharmacokinetics and Pharmacodynamics of Tenofovir 1% Gel Following Pericoital or Daily Gel Dosing

Version 1.0

April 24, 2012

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study: Coital PK/PD of Tenofovir Gel

INFORMED CONSENT

You are being asked to take part in this research study because you are a male 21 years of age or older and you have a female partner between the ages of 21 and 46 years. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). Approximately 40 heterosexual monogamous sexually-active couples who are currently not using condoms or any other barriers to prevent pregnancy or sexually transmitted infections will participate in this study. The product being used in this study is tenofovir 1% gel and is supplied by CONRAD.The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to join this study, we want you to know about the study.

This is a screening and enrollment consent form. This consent form provides you with information about the study, including information regarding screening exams and tests, including interview questions, urine and blood tests, a physical exam and an exam of your penis. You will receive information regarding what is expected of you if you are found to meet the study requirements and decide to enroll into MTN-011.

The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this form to keep.

YOUR PARTICIPATION IS VOLUNTARY

Before you learn about the study, it is important that you know the following:

- Your participation is voluntary: You do not have to take part in the study if you do not want to. If anyone has threatened you regarding your participation in this study you should notify study staff immediately.
- You may decide not to take part in the study, or to leave the study at any time, without losing your regular medical care.
- As part of this study, you will be asked to engage in penile-vaginal intercourse with your partner at specific visits.
- Both you and your partner must be eligible and agree to complete the study procedures. If any information is learned about you or your partner's health or behavior during the screening and enrollment or at any other visit, you may not be able to complete the rest of the scheduled study visits. Information you provide during your participation is confidential. Your test results and other personal information will not be shared with your partner, unless you specifically ask staff to provide your partner with this information, in which case you would need to provide written permission for these results to be shared.
- If you or your partner decides not to take part in the study, you can still join another study later, if one is available and if you qualify. You are asked to tell the study staff about any other studies you are taking part in, or thinking of taking part in.

PURPOSE OF THE STUDY

MTN-011 is testing one product, a gel that is put in the vagina called tenofovir gel. The main purpose of this study is to help researchers:

- Develop a better understanding of the impact of penile-vaginal intercourse on the absorption of tenofovir 1% gel when applied vaginally
- Examine how penile-vaginal intercourse in the presence of tenofovir 1% gel affects the vaginal environment
- Understand whether the gel is acceptable to users

Tenofovir gel is a drug being developed as a microbicide. A microbicide is a drug or agent that is capable of preventing HIV infection. Results from a study testing tenofovir gel, CAPRISA 004, were published in 2010. CAPRISA 004 was done to find out if tenofovir gel could protect women from getting HIV, and to test the gel's safety. The results of CAPRISA 004 showed that women who received tenofovir gel had a lower risk of getting HIV during the trial, compared to women who received placebo gel. Tenofovir gel also showed some protection against new cases of herpes. An additional study called, VOICE, asked women to use tenofovir gel daily. Tenofovir gel did not show a protective effect against HIV in VOICE. MTN-011 will help us to better understand the difference in results between VOICE and CAPRISA 004.

The United States Food and Drug Administration (US FDA) has been informed of this study and has permitted it to be conducted. [The [local authority] also has permitted the study to be conducted.]

This study will involve two sites in the United States. Including the screening period, you will be enrolled in this study for approximately 3 months.

STUDY PRODUCT and PROCEDURE OVERVIEW

If you and your partner are found to be eligible for this study you may continue to participate in this study. Your next visit will be your Enrollment Visit. You and your partner will need to return to the clinic for your study results and to undergo the next round of assessments. The timing of the Enrollment visit, your next visit, will depend upon your female partner's menstrual cycle. You will have a total of 6 clinic visits and your female partner will have a total of 13 visits.

A summary of the visit schedule is as follows, you will only be asked to attend the visits with an 'x' in the Couple Visit column:

Group 1						
Gel	**Visit**	**Visit Name**	**Couple Visit**	**Single Dose of Gel Before Sex/Visit**	**Sex**	**Single Dose of Gel After Sex**
	1	Screening	X			
	2a	Enrollment, No Gel/Sex	X		X	
	2b	Post-Sex Sampling				
-1 hr	3a	Gel -1/Sex	X	X	X	
	3b	Post-Sex Sampling				
	4a	Gel -1/No Sex		X		
	4b	Sampling				
-24 hr	5a	Gel -24/Sex	X	X	X	
	5b	Post-Sex Sampling				
	6a	Gel -24/No Sex				
	6b	Sampling				
BAT	7a	Gel -1/Sex/ Gel +1	X	X	X	X
	7b/ Final	Post-Sex Sampling	X			

You are not being asked to use a study product, but your female partner is being asked to dose with a single dose of tenofovir gel at multiple study visits and before and after sex at one visit. She will apply a single dose before you both engage in penile-vaginal intercourse at [SITES TO INSERT NAME OF HOTEL OR SIMILAR LOCATION].

WHAT DO I HAVE TO DO IF I TAKE PART IN THE SCREENING EXAMS AND TESTS?

The procedures done during the screening portion of this visit will take about [sites to insert time]. Not all of your results will be available right away. Study staff will inform you of your results at a future visit or when they become available.

- Study staff will ask you where you live and other questions about you, your medical health (including what medications you are taking), your sexual practices and your understanding of the study requirements.

- Study staff will:

  - Perform a physical exam

  - Talk with you about the requirements of the study including, but not limited to:
    - You must agree to engage in penile-vaginal intercourse with your current partner at specific visits at a specified location outside of the clinic, but nearby (hotel or similar location) [INSERT NAME OF HOTEL OR SIMILAR LOCATION] [INSERT CONFIDENTIALITY PROTECTION PROCEDURES.]
    - Agree to abstain from intercourse (oral, anal, or penile-vaginal) and other practices (e.g., masturbation, application of lubricants/ spermicides or other related practices) 72 hours prior to each follow-up visit
    - Not having a sexually transmitted infection (STI) in the past 6 months
    - Being in a monogamous relationship with your partner for six months and the intention to stay in this relationship for at least another 4 months

  - Perform a genital exam. This will involve an exam of the entire surface of your penis and your testicles, they will also check your lymph nodes.

  - Ask you to provide a semen sample.

  - Test your urine for infections passed through sex

  - Take a blood sample [Sites to insert amount]:
    - To test for infections passed through sex, including HIV
      - You will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we know your status for sure. You

must receive your HIV test results to be in the study. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.

- Give you treatment or refer you for treatment for infections passed through sex or other services, if needed.

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

- Schedule your next visit to enroll in MTN-011, if you are willing and eligible

ENROLLMENT and STUDY PROCEDURES

If you and your partner are found to be eligible for this study you may continue to participate in this study. Below you will find a summary of all of the procedures involved with confirming eligibility and participating in this study.

- Talk with study staff about the following:
    - Your medical health (including whether you have had any medical issues and what medications you are taking), at all visits
    - Where you live and other questions about you, at all visits except your final clinic visit
    - Your sexual practices and other questions from study staff to ensure that you are still allowed to continue in this study at all visits, except your final clinic visit
    - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex
    - The procedures you should follow during your sex visit

- You will be asked to:
    - Schedule your next visit, when needed (except at your final visit)
    - Answer questions about your participation in this study at some visits. These questions may be asked on a computer, the study clinic staff will provide you with instruction prior to using the computer

- The following clinical procedures will be performed:
    - Have a physical exam at most visits
    - Have a genital exam, if needed
    - You will be asked to provide a blood sample [Sites to insert amount]:
        - To save in the event there are any questions about your laboratory results at your Enrollment Visit
        - To test for infections passed through sex, including HIV at your Final Clinic Visit

- It is important that you know that you will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we know your status for sure. We will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.

As part of the clinic procedures you will:

- o Receive treatment or be referred for treatment for problems that the study staff may find.
- o Receive available test results from study staff

Finally, you and your partner will be asked to engage in intercourse on four occasions.

AT ANY TIME IN THE STUDY

If you have health problems or if there's any problem interpreting your laboratory tests or if there's any concern regarding your health you may need to:

- Have an exam of your genital area
- Give blood and/or urine, to test for infections passed through sex.
- Get treatment for most types of infections if you need it.

In the unlikely event that you become infected with HIV.
As described above, if you are thought to have HIV, you will have several tests to confirm your results. You will be asked to give additional blood (XX mL) for tests to examine the amount of HIV in your blood and whether any HIV in your blood is resistant to medications used to treat HIV. Results of the resistance tests will be provided if these are needed for your medical care.

If the HIV tests confirm that you or your partner have been infected with HIV, your partner will stop using gel, and your participation in the study will end.

Study staff will give you counseling and referrals for medical care and other services available to you. With your written permission, study staff may share information including test results that may be helpful to your health care provider.

RISKS AND/OR DISCOMFORTS

Whenever your blood is drawn, you may:

- Feel discomfort or pain when your blood is drawn.
- Feel dizzy or faint, but most people do not have this reaction.
- Have more than expected bleeding, a bruise, swelling, small clot, or infection where the needle goes in your arm or finger

When men have genital exams:

- Feel discomfort in having genital area examined
- Feel pressure
- Experience embarrassment

When you answer computer questions:
There are few risks to you from answering the computer questions. Your answers to the questions will be stored on a larger computer here at [study site] that can only be accessed by authorized study staff. Your answers then will be transferred to the same place where your study forms are sent. As with all of your study information, every effort will be made to keep your personal information confidential. Your answers will be identified by your study number only (not your name). However, absolute confidentiality cannot be guaranteed.

You could have these effects or other effects that we do not know about.

A small amount of tenofovir may pass from your partner to you.

Tenofovir gel was found to be well-tolerated in a study involving men who applied gel to the penis and left it on for 6-10 hours for seven consecutive days. The most side effects were mild pain (burning, irritation, discomfort) and itching.

Other Possible Risks:
We do not know if there are other risks if you use herbal treatments or supplements while you are using gel. Please tell study staff if you are using any herbal treatments or supplements.

You may become worried while waiting for your test results. 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. If you have HIV or other infections, knowing this could make you worried. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality while you are having the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your

STI and HIV status could also cause problems between you and your partner. Also, if your partner finds out that you have not been monogamous, this may cause problems in your relationship. Study staff will not disclose any information that you tell them to your partner, but it is possible that your partner may find out.

If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them if you would like.

BENEFITS

You may get no direct benefit from being in this study.

You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV prevention. This is true no matter what study group you are in.

You will have physical exams and genital exams. You will have tests to check on the health of your blood. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you.

You and your partner will get counseling and testing for HIV. If you or your partner have infections passed through sex, other than HIV infection, you will be offered or referred to a place where you can get medicine to treat them, if needed. This study does not provide medication for treatment of HIV/AIDS. If you become infected with HIV, you will be referred for medical care, counseling, and other services available to you.

There may be no direct benefits to you from answering the computer questions. However, information learned about the computer questions may help researchers improve the way they collect information about individuals' sexual behaviors.

NEW INFORMATION

You will be told any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the gel may be causing bad effects, or that clearly shows that the gel is very effective in protecting against HIV, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You and your partner may be withdrawn from the study without your consent if either of you:

- become pregnant (females)
- report having sexual intercourse with another person

- are not willing to find out your HIV test results.
- become infected with an infection passed through sex
- are not able to attend clinic visits or complete the study procedures.
- are taking certain medications
- are taking medication for possible recent exposure to HIV infection.
- are unable or unwilling to follow study procedures or instructions.
- could be harmed by continuing to take gel.

Or if:

- the study is stopped or canceled.
- the study staff feels that staying in the study would be harmful to you.
- other reasons, decided by the study staff.

It is important for you to know that if, at any time your partner is withdrawn from the study your participation in this study will also end.

If you or your partner withdraws early from the study, we will ask you to come in for an early termination visit, all of the procedures planned for the final clinic visit will take place at this time.

ALTERNATIVES TO PARTICIPATION

There are no gels known to protect against HIV during sex. The only known way to protect against HIV during sex is to use a condom every time you have sex.

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

COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you and/or your partner for infections passed through sex other than HIV will be provided free of charge by the study.

REIMBURSEMENT

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

CONFIDENTIALITY

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

Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert name of applicable Institutional Review Board (IRB), an IRB is a committee that watches over the safety and rights of research participants]
- study staff
- study monitors
- the organization that supplies tenofovir gel (CONRAD)

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

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

STORAGE AND FUTURE TESTING OF SPECIMENS

There might be a small amount of blood and other biological specimens left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your blood and other biological specimens for testing in future studies. You can still enroll in this study if you decide not to have blood and other biological specimens stored for future studies. If you do not want blood and other biological specimens stored, we will destroy the left over specimens. Any future studies that may be done will also have to be approved by an IRB.

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

Initial and date

_____ I **do not** agree to allow my biological specimens to be stored and health data to be used in future research studies.

Initial and date

RESEARCH-RELATED INJURY

[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 get additional treatment for your injuries. There is no program to pay money or give other forms of compensation either through this institution or the US National Institutes of Health (NIH) for research-related complications or injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

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

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB or other organization appropriate for the site] at [insert physical address and telephone number]. If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or Community Advisory Board (CAB) member [staff will decide which] at [insert physical address and telephone number].

SIGNATURES

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

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

APPENDIX VII: SAMPLE INFORMED CONSENT DOCUMENT GROUP 2 MALE SCREENING AND ENROLLMENT

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-011

Phase 1 Evaluation of the Impact of Coitus on the Pharmacokinetics and Pharmacodynamics of Tenofovir 1% Gel Following Pericoital or Daily Gel Dosing

Version 1.0

April 24, 2012

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study: Coital PK/PD of Tenofovir Gel

INFORMED CONSENT

You are being asked to take part in this research study because you are a male 21 years of age or older and you have a female partner between the ages of 21 and 46 years. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). Approximately 40 heterosexual monogamous sexually-active couples who are currently not using condoms or any other barriers to prevent pregnancy or sexually transmitted infections will participate in this study. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to join this study, we want you to know about the study.

This is a screening and enrollment consent form. This consent form provides you with information about the study, including information regarding screening exams and tests, including interview questions, urine, and blood tests, a physical exam and an exam of your penis. You will receive information regarding what is expected of you if you are found to meet the study requirements and decide to enroll into MTN-011.

The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this form to keep.

YOUR PARTICIPATION IS VOLUNTARY

Before you learn about the study, it is important that you know the following:

- Your participation is voluntary: You do not have to take part in the study if you do not want to. If anyone has threatened you regarding your participation in this study you should notify study staff immediately.
- You may decide not to take part in the study, or to leave the study at any time, without losing your regular medical care.
- As part of this study, you will be asked to engage in penile-vaginal intercourse with your partner at a specific visit.
- Both you and your partner must be eligible and agree to complete the study procedures. If any information is learned about you or your partner's health or behavior during the screening and enrollment or at any other visit, you may not be able to complete the rest of the scheduled study visits. Information you provide during your participation is confidential. Your test results and other personal information will not be shared with your partner, unless you specifically ask staff to provide your partner with this information, in which case you would need to provide written permission for these results to be shared.
- If you or your partner decides not to take part in the study, you can still join another study later, if one is available and if you qualify. You are asked to tell the study staff about any other studies you are taking part in, or thinking of taking part in.

PURPOSE OF THE STUDY

MTN-011 is testing one product, a gel that is put in the vagina called tenofovir gel. The main purpose of this study is to help researchers:

- Develop a better understanding of the impact of penile-vaginal intercourse on the absorption of tenofovir 1% gel when applied vaginally
- Examine how penile-vaginal intercourse in the presence of tenofovir 1% gel affects the vaginal environment
- Understand whether the gel is acceptable to users

Tenofovir gel is a drug being developed as a microbicide. A microbicide is a drug or agent that is capable of preventing HIV infection. Results from a study testing tenofovir gel, CAPRISA 004, were published in 2010. CAPRISA 004 sought to find out if tenofovir gel could protect women from getting HIV, and to test the gel's safety. The results of CAPRISA 004 showed that women who received tenofovir gel had a lower risk of getting HIV during the trial, compared to women who received placebo gel. Tenofovir gel also showed some protection against new cases of herpes. An additional study called, VOICE, asked women to use tenofovir gel daily. Tenofovir gel did not show a protective effect against HIV in VOICE. MTN-011 will help us to better understand the difference in results between VOICE and CAPRISA 004.

The United States Food and Drug Administration (US FDA) has been informed of this study and has permitted it to be conducted. [The [local authority] also has permitted the study to be conducted.]

This study will involve two sites in the United States. Including the screening period, you will be enrolled in this study for approximately 4 1/2 months.

STUDY PRODUCT AND PROCEDURE OVERVIEW

If you agree to participate and you and your partner are found to be eligible, you will be asked to return to the clinic and engage in penile-vaginal intercourse at [sites to insert location] after your female partner has dosed with gel daily, for seven days.

If you and your partner are found to be eligible for this study you may continue to participate in this study. Your next visit will be your Enrollment Visit. You and your partner will need to return to the clinic for your study results and to undergo the next round of assessments. The Enrollment Visit- Visit 2, will depend on your female partner's menstrual cycle. Females in this group will have a total of 11 visits. The men in this group will have 5 visits. A summary of the visit and product use schedule (females only) is provided below. You will only be asked to attend the visits with an 'X' in the Couple Visit column.

Group 2					
Gel	**Visit**	**Visit Name**	**Couple Visit**	**7 Daily Doses to be to be Used Before Sex/Visit**	**Sex**
	1	Screening	X		
	2	Enrollment- Provision of Study Product	X	X	
-1 hr	3a	Gel/Sex	X		X
	3b	Post-Sex Sampling			
	4	Provision of Study Product		X	
	5	Sampling			
-72 hr	6	Provision of Study Product		X	
	7a	Gel/Sex	X		X
	7b	Post-Sex Sampling			
	8	Provision of Study Product		X	
	9/ Final	Sampling	X		

WHAT DO I HAVE TO DO IF I TAKE PART IN THE SCREENING EXAMS AND TESTS?

The procedures done during the screening portion of this visit will take about [sites to insert time]. Not all of your results will be available right away. Study staff will inform you of your results at a future visit or when they become available.

- Study staff will ask you where you live and other questions about you, your medical health (including what medications you are taking), your sexual practices and your understanding of the study requirements.

- Study staff will:

  - Perform a physical exam

  - Talk with you about the requirements of the study including, but not limited to:
    - You must agree to engage in penile-vaginal intercourse with your current partner at specific visits at a specified location outside of the clinic, but nearby (hotel or similar location) [INSERT NAME OF HOTEL OR SIMILAR LOCATION] [INSERT CONFIDENTIALITY PROTECTION PROCEDURES.]
    - Agree to abstain from intercourse (oral, anal, or penile-vaginal) and other practices (e.g., masturbation, application of lubricants/ spermicides or other related practices) 72 hours prior to each follow-up visit and during home gel use
    - Not having a sexually transmitted infection (STI) in the past 6 months
    - Being in a monogamous relationship with your partner for six months and the intention to stay in this relationship for at least another 4 months

  - Perform a genital exam. This will involve an exam of the entire surface of your penis and your testicles, they will also check your lymph nodes.

  - Ask you to provide a semen sample.

  - Test your urine for infections passed through sex

  - Take a blood sample [Sites to insert amount]:
    - To test for infections passed through sex, including HIV
      - You will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we know your status for sure. You

must receive your HIV test results to be in the study. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.

- Give you treatment or refer you for treatment for infections passed through sex or other services, if needed.

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

- Schedule your next visit to enroll in MTN-011, if you are willing and eligible

ENROLLMENT and STUDY PROCEDURES

If you and your partner are found to be eligible for this study you may continue to participate in this study. Below you will find a summary of all of the procedures involved with confirming eligibility and participating in this study.

- Talk with study staff about the following:
    - Your medical health (including whether you have had any medical issues and what medications you are taking), at all visits
    - Where you live and other questions about you, at all visits except your final clinic visit
    - Your sexual practices and other questions from study staff to ensure that you are still allowed to continue in this study at all visits, except your final clinic visit
    - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex
    - The procedures you should follow during your sex visit

- You will be asked to:
    - Schedule your next visit, when needed (except at your final visit)
    - Answer questions about your participation in this study at your final clinic visit, some of these questions may be asked on a computer, the study clinic staff will provide you with instruction prior to using the computer

The following clinical procedures will be performed:

- Have a physical exam at most visits
- Have a genital exam, if needed
- You will be asked to provide a blood sample [Sites to insert amount]:
    - To be kept frozen and used, only if needed to check on your health or if there are questions about your lab tests at Visit 2 only

- To test for infections passed through sex, including HIV at your final clinic visit
    - It is important that you know that you will be told your HIV test result as soon as it is available. You will talk with the study staff about the meaning of your results, how you feel about them, and ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we know your status for sure. We will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.

As part of the clinic procedures you will:

- o Receive treatment or be referred for treatment for problems that the study staff may find.
- o Receive available test results from study staff

Finally, you and your partner will be asked to engage in intercourse on two occasions.

AT ANY TIME IN THE STUDY

If you have health problems or if there's any problem interpreting your laboratory tests or if there's any concern regarding your health you may need to:

- Have an exam of your genital area
- Give blood and/or urine, to test for infections passed through sex.
- Get treatment for most types of infections if you need it.

In the unlikely event that you become infected with HIV.

As described above, if you are thought to have HIV, you will have several tests to confirm your results. You will be asked to give additional blood (XX mL) for tests to examine the amount of HIV in your blood and whether any HIV in your blood is resistant to medications used to treat HIV. Results of the resistance tests will be provided if these are needed for your medical care.

If the HIV tests confirm that you or your partner have been infected with HIV, your partner will stop using gel, and your participation in the study will end.

Study staff will give you counseling and referrals for medical care and other services available to you. With your written permission, study staff may share information including test results that may be helpful to your health care provider.

RISKS AND/OR DISCOMFORTS

Whenever your blood is drawn, you may:

- Feel discomfort or pain when your blood is drawn.
- Feel dizzy or faint, but most people do not have this reaction.
- Have more than expected bleeding, a bruise, swelling, small clot, or infection where the needle goes in your arm or finger

When men have genital exams:

- Feel discomfort in having genital area examined
- Feel pressure
- Experience embarrassment

When you answer computer questions:
There are few risks to you from answering the computer questions. Your answers to the questions will be stored on a larger computer here at [study site] that can only be accessed by authorized study staff. Your answers then will be transferred to the same place where your study forms are sent. As with all of your study information, every effort will be made to keep your personal information confidential. Your answers will be identified by your study number only (not your name). However, absolute confidentiality cannot be guaranteed.

You could have these effects or other effects that we do not know about.

A small amount of tenofovir may pass from your partner to you.

Tenofovir gel was found to be well-tolerated in a study involving men who applied gel to the penis and left it on for 6-10 hours for seven consecutive days. The most side effects were mild pain (burning, irritation, discomfort) and itching.

Other Possible Risks:
We do not know if there are other risks if you use herbal treatments or supplements while you are using gel. Please tell study staff if you are using any herbal treatments or supplements.

You may become worried while waiting for your test results. 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. If you have HIV or other infections, knowing this could make you worried. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality while you are having the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your

STI and HIV status could also cause problems between you and your partner. Also, if your partner finds out that you have not been monogamous, this may cause problems in your relationship. Study staff will not disclose any information that you tell them to your partner, but it is possible that your partner may find out.

If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them if you would like.

BENEFITS

You may get no direct benefit from being in this study.

You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV prevention. This is true no matter what study group you are in.

You will have physical exams and genital exams. You will have tests to check on the health of your blood. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you.

You and your partner will get counseling and testing for HIV. If you or your partner have infections passed through sex, other than HIV infection, you will be offered or referred to a place where you can get medicine to treat them, if needed. This study does not provide medication for treatment of HIV/AIDS. If you become infected with HIV, you will be referred for medical care, counseling, and other services available to you.

There may be no direct benefits to you from answering the computer questions. However, information learned about the computer questions may help researchers improve the way they collect information about individuals' sexual behaviors.

NEW INFORMATION

You will be told any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the gel may be causing bad effects, or that clearly shows that the gel is very effective in protecting against HIV, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You and your partner may be withdrawn from the study without your consent if either of you:

- become pregnant (females).
- report having sexual intercourse with another person

- are not willing to find out your HIV test results.
- become infected with an infection passed through sex
- are not able to attend clinic visits or complete the study procedures.
- are taking certain medications
- are taking medication for possible recent exposure to HIV infection.
- are unable or unwilling to follow study procedures or instructions.
- could be harmed by continuing to take gel.

Or if:

- the study is stopped or canceled.
- the study staff feels that staying in the study would be harmful to you.
- other reasons, decided by the study staff.

It is important for you to know that if, at any time your partner is withdrawn from the study your participation in this study will also end.

If you or your partner withdraws early from the study, we will ask you to come in for an early termination visit, all of the procedures planned for the final clinic visit will take place at this time.

ALTERNATIVES TO PARTICIPATION

There are no gels known to protect against HIV during sex. The only known way to protect against HIV during sex is to use a condom every time you have sex.

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

COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you and/or your partner for infections passed through sex other than HIV will be provided free of charge by the study.

REIMBURSEMENT

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

CONFIDENTIALITY

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

Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert name of applicable Institutional Review Board (IRB), an IRB is a committee that watches over the safety and rights of research participants]
- study staff
- study monitors
- the organization that supplies tenofovir gel (CONRAD)

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

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

STORAGE AND FUTURE TESTING OF SPECIMENS

There might be a small amount of blood and other biological specimens left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your blood and other biological specimens for testing in future studies. You can still enroll in this study if you decide not to have blood and other biological specimens stored for future studies. If you do not want blood and other biological specimens stored, we will destroy the left over specimens. Any future studies that may be done will also have to be approved by an IRB.

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

Initial and date

_____ I **do not** agree to allow my biological specimens to be stored and health data to be used in future research studies.

Initial and date

RESEARCH-RELATED INJURY

[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 get additional treatment for your injuries. There is no program to pay money or give other forms of compensation either through this institution or the US National Institutes of Health (NIH) for research-related complications or injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

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

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB or other organization appropriate for the site] at [insert physical address and telephone number]. If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or Community Advisory Board (CAB) member [staff will decide which] at [insert physical address and telephone number].

SIGNATURES

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

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

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