MTN-014

A Phase 1 Crossover Trial Evaluating the Pharmacokinetics of Tenofovir Reduced-Glycerin 1% Gel in the Rectal and Vaginal Compartments in Women

Microbicide Trials Network

Funded by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine transaminase
API	active pharmaceutical ingredient
ART	antiretroviral therapy
AST	aspartate aminotransferase
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
BV	bacterial vaginosis
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	current good manufacturing practices
CHARM	Combination HIV Antiretroviral Rectal Microbicide
C_{max}	maximum concentration
CORE	Coordinating and Operations Center
CRF	case report form
CRS	Clinical Research Site
CT	Chlamydia trachomatis, chlamydia
CTA	Clinical Trial Agreement
CVL	cervicovaginal lavage
CWG	Community Working Group
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAIDS PRO	DAIDS Protocol Registration Office
DOD	direct observed dosing
DSMB	Data Safety Monitoring Board
EAE	expedited adverse event
EC	ethics committee
FDA	(US) Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
FTC	emtricitabine
G	grams
GC	Neisseria gonorrhoeae, gonorrhea
GCP	Good Clinical Practices
GEE	Generalized Estimating Equations
GRFT	griffithsin
hCG	human chorionic gonadotropin
HEC	hydroxyethylcellulose
HEENT	Head, Eye, Ear, Nose and Throat
HIV	Human Immunodeficiency Virus

HPTN	HIV Prevention Trials Network
HSV-2	Herpes simplex virus type 2
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Conference on Harmonisation
ICRR	incidence rate ratio
IRB	Institutional Review Board
IND	investigational new drug
IoR	Investigator of Record
IV	Intravenous
IUD	intrauterine device
KOH	potassium hydroxide
kg	kilogram
LC/MS	liquid chromatography-mass spectometry
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantification
µg	microgram
mg	milligram
mL	milliliter
MO-DCs	human monocyte-derived dendritic cells
MTN	Microbicide Trials Network
MTT	(3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole)
MSM	men who have sex with men
NAAT	nucleic acid amplification test
ng	nanogram
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NL	network laboratory
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NOAEL	no-observed-adverse-effect-level
OHRP	Office for Human Research Protections
PAMA	Pediatric, Adolescent and Maternal AIDS
PBMC	peripheral blood mononuclear cell
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PD	pharmacodynamics
PEP	post-exposure prophylaxis
PK	pharmacokinetics
pmol	picomole
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development, Inc.
PrEP	Pre-exposure prophylaxis
PRO	Protocol Registration Office
PSRT	Protocol Safety Review Team
PSS	polystyrene sulfonate
PTID	participant identification

RAI	Receptive anal intercourse
RE	Regulatory Entity
RG	reduced-glycerin
RMP	Rectal Microbicide Program
RNA	ribonucleic acid
RT	reverse transcriptase
RTI	reproductive tract infection
RT-PCR	real-time polymerase chain reaction
RSC	Regulatory Support Center
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDMC	Statistical Data Management Center
SHIV	simian-human immunodeficiency virus
SMC	Study Monitoring Committee
SOP	standard operating procedure
SSP	study specific procedures
STD	sexually transmitted diseases
STI	sexually transmitted infection
SUSARs	Suspected, unexpected serious adverse reactions
TDF	tenofovir disoproxil fumarate
TER	transepithelial resistance
TERIS	Teratogen Information System
TFV	tenofovir
UA	urinalysis
UCLA	University of California, Los Angeles
ULN	upper limits of normal
UNAIDS	United Nations Programme on HIV/AIDS
UPMC	University of Pittsburgh Medical Center
USA	United States of America
UTI	urinary tract infection
wt	wild-type
w/w	weight/weight
WHO	World Health Organization

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MTN-014

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INVESTIGATOR SIGNATURE FORM

Version 2.0

May 1, 2013

A Study of the Microbicide Trials Network

Funded by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
US National Institute of Mental Health
US National Institutes of Health

IND Holder:
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. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, CONRAD and other entities for review prior to submission, as required by the MTN Publication Policy.

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

_____
Name of Investigator of Record

_____ _____
Signature of Investigator of Record Date

MTN-014

A Phase 1 Crossover Trial Evaluating the Pharmacokinetics of Tenofovir Reduced-Glycerin 1% Gel in the Rectal and Vaginal Compartments in Women

PROTOCOL SUMMARY

Short Title: Tenofovir Levels Following Local Application of Tenofovir Reduced-Glycerin 1% Gel

Clinical Phase: Phase 1

IND Sponsor: CONRAD

Protocol Chair: Gonasagrie Nair, MBChB

Protocol Co-Chair: Jessica Justman, MD

Sample Size: Approximately 28 women

Study Population: Healthy, HIV uninfected, non-pregnant women aged 21 to 45 years (inclusive)

Study Sites: Sites selected by the MTN Executive Committee

Study Design: Phase 1, two-arm, crossover, randomized trial (1:1)

Study Duration: Accrual will require approximately 10 months per site. Each enrolled participant will be followed for approximately 10-13 weeks, depending upon their menses schedule.

Study Product:

- Tenofovir (TFV) reduced-glycerin (RG) 1% gel

Study Regimen:

	N	Period 1 Once daily application of TFV RG 1% gel 2 Weeks	Washout ~6 weeks	Period 2 Once daily application of TFV RG 1% gel 2 Weeks
Sequence A	14	Vaginal		Rectal
Sequence B	14	Rectal		Vaginal

Primary Objectives:

1. To compare local and systemic pharmacokinetics of tenofovir reduced-glycerin 1% gel after 2 weeks of daily rectal use and after 2 weeks of daily vaginal use

Primary Endpoints:

1. The pharmacokinetic endpoints are drug levels in:

    - Blood
    - Vaginal fluid samples
    - Cervical cytobrush
    - Rectal fluid samples
    - Cervicovaginal lavage
    - Vaginal tissue
    - Rectal tissue

    Note: All US participants (approximately 14 total) will supply vaginal and rectal tissue samples. See Section 7.14 for additional details.

Secondary Objective:

1. To assess the safety of tenofovir reduced-glycerin 1% gel after 2 weeks of daily rectal use and after 2 weeks of daily vaginal use

Secondary Endpoint:

1. The safety endpoint is:

    - Adverse events Grade 2 or higher as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009), Addendum 1, Female Genital Grading Table for Use in Microbicide Studies, and Addendum 3, Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012)

Exploratory Objectives:

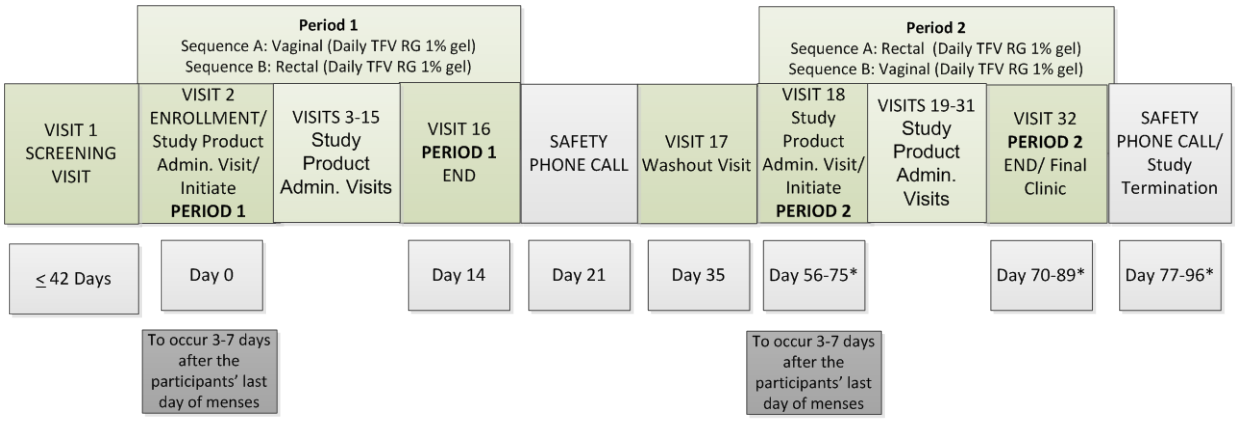
1. Correlate drug levels in rectal and genital fluids with drug potency

2. Determine changes in microflora, biomarkers and gene expression from the vaginal and rectal environments after 2 weeks of daily rectal versus 2 weeks of daily vaginal use of tenofovir reduced-glycerin 1% gel at sites with capacity

Exploratory Endpoints:

- Inhibition of HIV by drug in rectal and genital fluids
- Changes in pH, microflora, biomarkers and gene expression

Figure 1: Study Visit Schedule



* Visit schedule will vary based upon participants' menses.

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	A Phase 1 Crossover Trial Evaluating the Pharmacokinetics of Tenofovir Reduced-Glycerin 1% Gel in the Rectal and Vaginal Compartments in Women
Protocol Number:	MTN-014
Short Title:	Tenofovir Levels Following Local Application of Tenofovir Reduced-Glycerin 1% Gel
Date:	May 1, 2013

1.2 Sponsor and Monitor Identification

Funding Agencies:	US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH) 6700 B Rockledge Drive Bethesda, MD 20892 USA US National Institute of Mental Health (NIMH) 6001 Executive Boulevard Rockville, MD 20852 USA US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)/NIH Pediatric, Adolescent and Maternal AIDS (PAMA) Branch 6100 Executive Boulevard Bethesda, MD 20892 USA
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2 INTRODUCTION

2.1 Oral Pre-Exposure Prophylaxis and Microbicides in HIV/AIDS Prevention

Thirty years into the Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) epidemic, the search for safe and effective methods of HIV prevention continues. While HIV incidence continues to remain steady in many areas of the world, the overwhelming majority of new HIV infections are occurring among women in sub-Saharan Africa. Increasing availability of antiretroviral therapy (ART) for infected persons will not address this, because the pace of new infections exceeds that of treatment initiation by a ratio of 2:1, at best.[1] Although male circumcision appears to provide considerable protection against HIV infection in men,[2,3] and when adopted widely, should reduce risk of HIV transmission at the population level, the benefit to vulnerable women will not begin to accrue for several years, even with widespread uptake of this procedure.[2]

In 2010, the results of the first clinical trial to demonstrate effectiveness were released. The CAPRISA 004 study demonstrated a 39% reduction in HIV acquisition, incidence rate ratio (IRR) = 0.61, 95% CI: 0.4-0.94, among participants who used tenofovir (TFV) 1% gel in a pericoital regimen. However, the daily dosing regimen of TFV 1% gel used in the MTN-003 (VOICE) Phase 2B effectiveness study was shown not to reduce rates of HIV acquisition compared to the matching placebo.[3, 4] These results speak to the daunting challenge of preventing HIV acquisition in females at high risk for HIV acquisition.

Addressing factors that could compromise the effectiveness of vaginal gel application is critical to the success of future trials. Receptive anal intercourse (RAI) is a concern especially if the prevalence of anal sex among heterosexual women is common. RAI is associated with increased risk of HIV acquisition among men who have sex with men (MSM)[5] and heterosexual women. The risk of HIV infection among high risk heterosexual women, who practice RAI (commercial sex workers) in South Africa has been found to be 2.3 times higher in comparison to women who did not practice anal intercourse in the same cohort of women.[6] While the rates of lifetime engagement of RAI vary by geographic location, some estimates from the United States and South Africa are provided, here. Among commercial sex workers, the prevalence of RAI in South Africa has been reported to be in excess of 40%.[7] Among female adults aged 25–44 in the United States, about 36% reported ever having receptive anal sex based on the 2006–2008 National Survey of Family Growth.[8] The same survey found that in high-risk areas of New York City, as much as 38% of women engaged in unprotected anal intercourse during the past year. Women are approximately seven times more likely than MSM to engage in unprotected receptive anal intercourse.[9] This coupled with the high lifetime rates of RAI, may result in a significant proportion of heterosexual HIV transmission occurring through RAI. Development of a safe and effective microbicide that can protect individuals who engage in RAI is critical. A product that

could provide a protective effect in both the vaginal and the rectal compartments is needed.

The vaginal and rectal application of tenofovir (TFV) reduce-glycerin (RG) 1% gel, a potential dual compartment microbicide will be tested in MTN-014.[10] Vaginal and rectal pharmacokinetic data is available when male and female participants apply either the original or the reduced-glycerin formulations of tenofovir gel rectally or vaginally. However, there is limited human data regarding tenofovir levels in the rectal compartment following vaginal application and levels in the vaginal compartment following rectal application. Recently, a non-human primate study showed significant levels tenofovir and tenofovir diphosphate in secretions and tissues of animals dosed either vaginally or rectally in the complementary compartment.[11] This finding suggests that the vaginal application of tenofovir gel could be effective for HIV-1 prevention in women who engage in RAI. Additionally, human rectal fluid samples collected from females who dosed with TFV 1% gel were found to be as high as or higher than concentrations measured in the oral only dosing period.[12]

MTN-014 will evaluate drug concentrations in the vaginal and rectal environments following administration of TFV RG 1% gel in each compartment.

2.2 *In vitro* and *Ex vivo* Studies

2.2.1 *In vitro* and *Ex vivo* Studies of TFV Gel (Various Formulations)

Formulation Testing

The original formulation, used in all vaginal microbicide tenofovir gel studies, was associated with gastrointestinal intolerance when applied rectally in a previous rectal microbicide study (RMP-02/MTN-006).[13] These AEs were thought to be potentially linked to the high osmolality of the TFV 1% gel (original vaginal formulation) (3111 mOsm/kg). Consequently, a new formulation of TFV 1% gel was developed with a reduced level of glycerin (RG). The TFV RG 1% gel has lower osmolality (846 mOsm/kg) than the TFV 1% gel (original vaginal formulation).[10]

From the current good manufacturing practice (cGMP) formulators, DPT Pharmaceuticals, the density of the TFV 1% gel is 1.06 g/mL and the TFV RG 1% gel is 1.02 g/mL. Each gram of gel contains 10 mg of tenofovir, and with the final calculated amount per dose rounded, this results in ~42 mg of tenofovir per dose for the TFV 1% gel and ~41 mg for the TFV RG 1% gel.

Condom Integrity

Information regarding condom integrity can be found in the Investigator's Brochure.[14]

Safety Testing in Cell Lines

Safety testing of the TFV RG 1% gel in epithelial cell lines has demonstrated retention of transepithelial resistance (TER) by Caco-2 and HEC-1-A cell lines, unlike the TFV 1% gel, which induced a transient drop in the epithelial resistance. The TER is the

resistance that develops once a cell monolayer grows to confluence. A fall in TER that occurs after product exposure may indicate that the product (e.g. N-9) has cellular toxicity. These data suggest that the TFV RG 1% gel may be less toxic to the rectal epithelium than the original TFV 1% gel.[10, 15]

Safety Testing in Ex vivo Explant Cultures

Preclinical testing of the TFV RG 1% gel and TFV 1% gel was done in colorectal explants. Due to the hyperosmolality of the original TFV 1% gel, colorectal and ectocervical explant tissue exhibited epithelial sloughing and fracture after exposure to the gel. The original TFV 1% gel had no effect on overall tissue viability as measured by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole). These data suggested that the tenofovir gel did not affect the viability of the tissue, but damaged the epithelium. Subsequent work of the TFV RG 1% gel in colorectal and ectocervical tissue showed no damage to the epithelium by histology and retention of tissue viability as measured by MTT.[10] Additional testing in colorectal and ectocervical explant cultures also showed the TFV RG 1% gel did not compromise product efficacy. Collectively, these data suggest the TFV RG 1% gel is just as effective as the original TFV 1% gel but is safer to the rectal epithelium.

Resistance, and Cross-resistance

HIV-1 isolates with reduced susceptibility to unformulated tenofovir have been selected in vitro.[16, 17] These viruses expressed a K65R mutation in reverse transcriptase (RT) and showed a 2-4 fold reduction in susceptibility to tenofovir.

Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognized.[16, 18] The M184V/I and/or K65R substitutions selected in vitro by the combination of FTC and unformulated TDF are also observed in some HIV-1 isolates from subjects failing treatment with TDF in combination with either lamivudine (3TC) or FTC, and either abacavir, didanosine, or zalcitabine.

2.3 Animal Studies

2.3.1 TFV RG 1% Gel

Rohan and colleagues conducted the first study to evaluate the rectal toxicity of the TFV RG 1% gel.[14] Male and female New Zealand rabbits were administered TFV 1% gel and TFV RG 1% gel once a day for 28 consecutive days, at a dose volume of 1 mL. The only microscopic findings judged to be related to study-product involved males administered TFV RG 1% gel. Findings in these groups consisted of minimal to mild depletion of secretory material from the mucosal cells and goblet cells of the rectum visible microscopically. However, there was no apparent atrophy of the epithelium. This finding was not considered to be adverse. Tenofovir 1% gel, and TFV RG 1% gel did not result in systemic or local toxicity when administered rectally for 28 consecutive days.

2.4 Clinical Studies

2.4.1 TFV 1% Gel (Original Formulation)

Pharmacokinetics

Vaginal Administration

A Phase 1 Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel, also known as HIV Prevention Trials Network (HPTN) 050, examined the PK of tenofovir gel.[19] Eighty-four (60 HIV negative and 24 HIV positive) women applied either 0.3% or 1% tenofovir gel once or twice daily for 14 days. Systemic absorption after use of 1% tenofovir gel was detected in 14 of the 25 women studied (limit of assay quantification: 3 ng/mL), and those with detectable levels of the drug showed evidence of only limited absorption (maximum serum levels: 3.1-25.8 ng/mL).[14]

A randomized trial to assess anti-HIV activity and soluble mucosal immunity following application of tenofovir gel provided data on the PK of tenofovir gel in cervicovaginal lavage (CVL) fluid. With daily dosing, 12 participants had 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.[20]

A Phase 2 study of TFV 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. 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. 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.[21]

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. Participants took a randomized sequence of oral tenofovir, TFV 1% gel, or a combination of both, for three 6-week study periods. The total length of time on study was 21-weeks, with the washout periods. Vaginal tissue drug levels were found to be 2 $\log_{10}$ higher after vaginal dosing compared to oral dosing.[12] In a subset of US participants (n= 72), vaginal tissue levels for the combination product use period were similar to those measured in the vaginal TFV 1% gel dosing period. Additionally, rectal fluid was collected during the vaginal TFV 1% gel dosing period at one US site (n= 12). The rectal fluid tenofovir concentrations were found to be as high as or higher than concentrations measured in the oral only dosing period.

CONRAD completed a Phase 1 trial to assess the local and systemic exposure of extracellular TFV and intracellular tenofovir diphosphate (TFV-DP) after a single application and after 14 days of once- or twice-daily TFV 1% gel application.[22] During the single-dose period, forty-nine women were randomized to the collection time point [0.5, 1, 2, 4, 6, 8, or 24 hr(s) after the single dose]. After the completion of the single-dose phase and a washout period, forty-seven participants dosed for two weeks. Women were randomized to a once- or twice-daily regimen and to the sample collection time points [4, 8 or 24 hrs after the final dose]. Minimal systemic absorption was observed with a median C_{max} at 4.0 and 3.4 ng/mL in the single-dose and multiple-dose groups, respectively (C≤29 ng/mL). Genital tract concentrations persist for up to 24 hours post-dose in both groups, with TFV concentrations in aspirates and tissue after a single-dose and multiple-doses, ranging from $1.2x10^4$ to $9.9x10^6$ ng/mL and $2.1x10^2$ to $1.4x10^6$ ng/mL, respectively. Tissue concentrations were well within the range of *in vitro* anti-HIV-1 EC_{50} (0.4-8.5μM). TFV-DP concentrations were high in endocervical cells ($7.1x10^3$ to $8.8x10^6$ ng/mL) and detectable in approximately 40% of the tissue samples ($1.8x10^2$ to $3.5x10^4$ ng/m).

Rectal Administration

In a Phase 1 study, RMP-02/MTN-006, 12 men and women participants received sequentially: single-dose oral TDF, single-dose TFV 1% gel (original vaginal formulation) per rectum, 7 daily doses of TFV 1% gel (original vaginal formulation) per rectum. Blood, tissue, and luminal sampling followed each of these 3 dosing periods. At 30 minutes following single rectal, topical dosing, rectal tissue concentrations were 100-times greater than 30 minutes after single oral dosing. Multiple rectal doses resulted in five times greater concentrations in tissue when compared to a single rectal dose with no significant increase in plasma concentrations. Peripheral blood mononuclear cell (PBMC) tenofovir-diphosphate (TFV-DP) concentrations were below limits of quantitation in the vast majority of specimens collected in the 24 hours following a single rectal dose.[13] In addition, tenofovir was detected in a proportion of vaginal samples collected from female participants.

Safety

Vaginal Administration

In HPTN 050, the TFV 1% gel formulation was well tolerated in both HIV-uninfected and -infected women.[23] Ninety-two percent of participants reported at least one AE, the majority 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 Grade 3 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.

In HPTN 059, 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.[21] 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.

In MTN-001, all three study regimens (TDF 300 mg tablet, TFV 1% gel and a combination of the TDF 300 mg tablet and TFV 1% gel) were well tolerated and found to be acceptable. More women preferred daily oral tenofovir to daily tenofovir vaginal gel (57% vs 28%), a difference largely driven by the preferences of women from the US sites (72% vs 14%). Self-reported adherence across sites was high (94%).[12]

In MTN-002, the first microbicide trial to be conducted during pregnancy, 16 women received a single vaginal dose of TFV 1% gel prior to elective cesarean section. [24] Blood, amniotic fluid, cord blood, endometrial tissue, and placental tissue were collected from participants. Plasma tenofovir levels were compared to historical controls. Study results demonstrated that tenofovir levels following a single vaginal dose of TFV 1% gel in pregnant women were similar to those found in non-pregnant women, and that plasma levels were 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 a single dose of tenofovir gel is safe in term pregnancy and warrants additional investigation of repeat dosing during pregnancy. No adverse pregnancy outcomes related to study product were noted.

In CAPRISA 004, there were no SAEs deemed related to the use of study product.[25] No renal disorders were observed in the study. Mild, self-limiting diarrhea was more common among women who used tenofovir gel (16.9 %) compared to women who used the placebo gel (11%). 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.

Penile Administration

In a male tolerance study (CONRAD A04-099/IND 73,382), TFV 1% gel was well tolerated in men following seven days of once daily exposure, for 6 to 10 hours, to the penis.[26] There were few reported and observed genital findings after product use including mild pain (burning, irritation, discomfort) and pruritus. All observed findings were classified as mild, small in number 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.

Rectal Administration

RMP-02/MTN-006 participants took a single oral dose of tenofovir disoproxil fumarate and applied a single rectal dose of TFV 1% gel (original vaginal formulation) or placebo

gel before applying the same gel again for 7 days. This study made comparisons between the vaginally-formulated original TFV 1% gel and a single dose oral tenofovir tablet in 18 HIV-seronegative participants randomized 2:1 to active product or placebo. Single-dose topical exposure of the TFV 1% gel showed no increase in AEs compared with placebo. After 7-days of exposure to TFV 1% gel, a total of 53 AEs were reported with all 12 participants reporting at least one event [41 Grade 1 AEs were reported in 12 participants, 6 Grade 2 AEs in 3 participants, and 6 Grade 3 AEs in 2 participants]. The majority of these were gastrointestinal. Conversely, there were significantly fewer AEs reported in the 6 participants randomized to placebo (HEC) [8 Grade 1 AEs in 4 participants and 1 Grade 2 AE in 1 participant] were reported. These findings support the use of a reduced-glycerin formulation in future rectally-applied tenofovir gel clinical trials.[13]

Effectiveness for Prevention of HIV

CAPRISA 004
The CAPRISA 004 trial was a Phase 2B trial that was designed to assess the effectiveness and safety of a TFV 1% gel, for the prevention of HIV acquisition in women.[25] 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.

VOICE
The daily dosing regimen of TFV 1% gel (original vaginal formulation) used in the MTN-003 (VOICE) Phase 2B effectiveness study was not shown to be associated with reduced rates of HIV acquisition and the VOICE DSMB recommended that this arm of the VOICE study be stopped early for futility.[3, 4]

2.4.2 TFV RG 1% Gel

Pharmacokinetics

Vaginal Administration
No vaginal administration studies have been completed to date. MTN-014 will supply these data.

Rectal Administration
To date, no studies have been completed that specifically assess the pharmacokinetics of TFV RG 1% gel, however MTN-014 and CHARM-01 (IPCP-HTM program), a planned Phase 1 rectal safety, acceptability, and PK/PD study will provide these data.

Participants in the CHARM-01 study will receive seven daily doses of the original TFV 1% gel, the TFV RG 1% gel, and a new rectal specific formulation of TFV 1% gel.

Safety

Rectal Administration

In addition to the recently completed MTN-007 study described below, two Phase 1 and one Phase 2 rectal-administration studies will evaluate TFV RG 1% gel. In addition, two studies outside of the MTN, Project GEL and CHARM-01, will collect safety data. MTN-017, a Phase 2 study, will evaluate the safety and acceptability of rectally-applied TFV RG 1% gel across multiple international sites.

MTN-007 was designed to assess the safety, adherence, and acceptability of TFV RG 1% gel. A nonoxynol-9 (N9) arm was included as a positive control for the mucosal safety assays. Sixty-five participants (45 men and 20 women) aged 18-61 were recruited from three US sites; Pittsburgh (PA), Birmingham (AL), and Boston (MA). Participants were randomized 1:1:1:1 to receive TFV RG 1% gel, HEC placebo gel (HEC), 2% nonoxynol-9 gel (N9), or no treatment (No Rx).[27] Participants were evaluated at Baseline, after a single dose, and after 7 daily doses of study product. Systemic and mucosal safety, acceptability, and adherence were evaluated at all three visits. Comprehensive mucosal safety evaluation included histology, fecal calprotectin, epithelial sloughing, cytokine expression (mRNA and protein), flow cytometry of mucosal T cell phenotype, and rectal microflora. All mucosal assays were performed on biopsies collected at 9 and 15 cm from the anal margin. Acceptability and adherence were determined by computer-administered questionnaires and interactive telephone response respectively. A total of 16 (TFV), 17 (HEC), 16 (N9), and 16 (No Rx) sexually abstinent participants were enrolled in the study. Product adherence was ≥ 94%. AEs were generally mild (G1: N=121 (80%)) or moderate (G2: N=27 (18%)). Two G3 and one G4 events occurred in the no treatment arm or before product use. There was no significant difference in the prevalence of AEs across the four arms of the study. Based on the MTN-007 data, the TFV RG 1% gel was well tolerated.[27]

2.5 Rationale for Study Design

Existing literature indicates that the practice of unprotected receptive anal intercourse amongst heterosexual women is significant. MTN-014 will evaluate drug concentrations in the vaginal and rectal environments following administration of TFV RG 1% gel in the opposite compartment. The crossover design will control for heterogeneity in the study population as well as intra-individual variability allowing for increased precision of the observations. A further advantage of this design is that the required sample size is halved, as each participant acts as a corresponding control.

2.6 Justification of Dosing

Tenofovir 1% Gel Daily Dosing

The selection of the reduced glycerin TFV 1% gel concentration for MTN-014 is based on both animal and clinical evidence suggesting an appropriate safety profile and potency.

The tolerability of the vaginal formula TFV 1% gel was confirmed in CAPRISA 004. Efficacy data from CAPRISA 004 showed that TFV 1% gel reduced HIV acquisition by an estimated 39% overall (p=0.017), however VOICE showed no reduction. The vaginal formulation of TFV 1% gel concentration is currently being evaluated in MTN-003 (IND 55,690), MTN-008 (IND 55,690), CONRAD A10-113 and A10-114 (IND 73,382) and, via pregnancy registry in MTN-016 and MTN-011 (IND 73,382). The reduced glycerin formulation applied rectally was found to be well tolerated in MTN-007 and is currently being studied in CHARM, Project GEL, and is planned for MTN-017 (IND 73,382).

Given the safety and efficacy data-to-date on TFV 1% gel, MTN-014 will provide initial bridging PK data for TFV RG 1% gel formulation as a potential dual compartment microbicide.

2.7 Justification of Directly Observed Dosing Strategy

MTN-014 will employ a directly observed dosing (DOD) strategy to ensure complete compliance to the study product regimen.

This strategy is being employed given recently obtained data from MTN-003 VOICE where tenofovir gel adherence as reported via unused applicator counts and by participant self-reports, was high, 86% and 90%, respectively.[4] However, in a case-cohort subset, adherence was low as demonstrated by the detection of tenofovir in an average of 25% of available quarterly plasma samples among participants randomized to tenofovir gel.[4]

DOD will guarantee that study participants receive the study product daily, ensuring that adherence does not serve as a confounding factor in the PK analysis. Protocol provisions have been made for study product administration outside of the clinic with/without DOD in the event that participants are unable to present to the clinic, See Section 6.0, *Study Product*, for additional details.

2.8 Other Protocol Considerations

Washout Period

The washout period for MTN-014 is based on toxicity, PK, and menstrual cycle concerns. A sufficient period of time is required to ensure that all drug from the first

period be essentially cleared from each participant to avoid any symptom carryover to the second period. Several studies of vaginal TFV gel dosing have demonstrated a 2 day half-life for TFV in blood, tissue, and luminal (vaginal and rectal) samples. Accordingly, with the passage of 14 days, the concentration will fall to less than 1% of the peak value following the last dose. So, given the variation in drug clearance and the potential impact of the menstrual cycle on TFV absorption and clearance, the samples will be collected at the same time of the menstrual cycle for each period. Therefore, once a decision was made to extend the washout period beyond 2 weeks, the protocol team committed to an approximate 6 week washout period to allow for sampling at the same time in the menstrual cycle.

Justification for the use of a Flexible Sigmoidoscope to Collect Rectal Biopsies in a Subset of Participants.

Rectal biopsies will be collected in a subset of participants using a flexible sigmoidoscope. A flexible sigmoidoscope allows for the collection of a sufficient number of rectal biopsies (6) at the preferred distance from the anal verge (~15-20 cm). An anoscope cannot extend beyond 5-9 cm and will not be used to collect biopsy samples. Further, in a previously completed trial, RMP 002/MTN-006, samples were collected at ~15-20 cm, and the collection of samples at this location will allow for a comparison between data generated in MTN-014 and the former.

3 OBJECTIVES

3.1 Primary Objective

1. To compare local and systemic pharmacokinetics of tenofovir reduced-glycerin 1% gel after 2 weeks of daily rectal use and after 2 weeks of daily vaginal use

3.2 Secondary Objective

1. To assess the safety of tenofovir reduced-glycerin 1% gel after 2 weeks of daily rectal use and after 2 weeks of daily vaginal use

3.3 Exploratory Objectives

1. Correlate drug levels in rectal and genital fluids with drug potency

2. Determine changes in microflora, biomarkers and gene expression from the vaginal and rectal environments after 2 weeks of daily rectal versus 2 weeks of daily vaginal use of tenofovir reduced-glycerin 1% gel at sites with capacity

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-014 is a Phase 1, multi-site, randomized two-sequence, two-period open label crossover study.

4.2 Summary of Major Endpoints

1. The pharmacokinetic endpoints are drug levels in:

    - Blood
    - Vaginal fluid samples
    - Cervical cytobrush
    - Rectal fluid samples
    - Cervicovaginal lavage
    - Vaginal tissue
    - Rectal tissue

    Note: All US participants (approximately 14 total) will supply vaginal and rectal tissue samples. See Section 7.14 for additional details.

4.3 Description of Study Population

The study population will be healthy, HIV-uninfected, non-pregnant women aged 21 to 45 years (inclusive) who meet the criteria outlined in Section 5.

4.4 Time to Complete Accrual

Accrual is expected to be complete in approximately 10 months per site.

4.5 Study Groups

Approximately 28 women will be randomized equally across 2 sequences. All study participants will complete a 14 day study period each of rectal and vaginal dosing in a randomly assigned order.

4.6 Sequence and Duration of Participation

The total duration of participation from the Enrollment Visit to Termination is anticipated to be 10-13 weeks, depending upon participants' menses schedule; this includes two two-week study product use periods and one six-week washout period plus a one-week follow-up safety phone call after the Period 2 End Visit. Visits may be completed within

specified windows around target dates. Detailed information regarding visit windows will be thoroughly described in the MTN-014 SSP Manual.

4.7 Sites

Sites approved by the MTN Executive Committee will participate in MTN-014.

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

Participants will be recruited from a variety of sources across sites, including family planning clinics and gynecology clinics, as well as community-based locations. 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. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use. Site community representatives should advise on these materials before they are submitted to the IRB/EC for review.

5.1.2 Retention

Once a participant is enrolled in MTN-014, the study site will make every effort to retain the participants in follow-up to minimize possible bias associated with loss-to-follow-up. An average retention rate of 95% will be targeted at each site. Each study site will be responsible for developing and implementing local Standard Operating Procedures (SOPs) to ensure and target high rates of retention.

5.2 Inclusion Criteria

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

1) Age 21 through 45 years (inclusive) at Screening, verified per site SOP

2) Able and willing to provide written informed consent

3) Able and willing to comply with all study procedure requirements, including, clinical and laboratory assessments, vaginal and rectal examinations, urine and blood testing, as well as attendance at all scheduled study visits

4) In general good health at Screening and Enrollment as determined by the Investigator of Record (IoR)/ or designee

5) Negative pregnancy test at Screening and Enrollment

6) HIV-negative at Screening and Enrollment, per applicable protocol algorithm in Appendix II

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

8) Willingness to use study-provided male condoms for the duration of study participation for penetrative intercourse

9) Per participant report at Screening, 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, progesterone-containing IUDs or extended use of oral contraceptives)

10) Per participant report at Enrollment, using an effective method of contraception and intending to use an effective method for the duration of study participation; these include:

- Hormonal methods, excluding vaginal rings
- Intrauterine device (IUD) inserted at least 42 days prior to Enrollment (but not past the maximum length of recommended usage according to package instructions)
- Sterilization of participant or partner at least 42 days prior to Enrollment
- Self-identifies as a woman who has sex with women exclusively
- Sexually abstinent for the at least 90 days prior to enrollment and the intention to remain sexually abstinent for the duration of study participation

11) Per participant report at Screening, states a willingness to refrain from inserting any non-study vaginal or rectal products or objects into the vagina or rectum, including but not limited to, spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), vaginal/rectal douches, enemas, non-study approved lubricants, sex toys (vibrators, dildos, etc.), and tampons for the duration of the study product use periods and for 24 hours prior to Period Initiation Visits and Period End Visits.

12) Pap result consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) or satisfactory evaluation of non-Grade 0 Pap result with no treatment required per clinical judgment of IoR or designee in the 12 calendar months prior to the Enrollment Visit

13) At Screening, participant agrees not to take part in other research studies involving drugs, medical devices, or vaginal/rectal products for the duration of study participation (including the time between the Screening and Enrollment visits)

Participants in the biopsy subset must also meet the following criteria at Screening to be eligible for inclusion:

14) Willing to abstain from inserting any non-study products into the vagina or rectum for 72 hours prior to and following the collection of biopsies.

15) Willing to abstain from vaginal and rectal intercourse 72 hours prior to and following the collection of biopsies.

16) Willing to restrict the use of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and/or other drugs that are associated with the increased likelihood of bleeding following mucosal biopsy collection for 72 hours prior to and following the collection biopsies

5.3 Exclusion Criteria

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

1) Participant report of any of the following:

   a) Known adverse reaction to the study product (ever)
   b) Known adverse reaction to latex (ever)
   c) Current male sex partner with known history of adverse reaction to latex (ever)
   d) History of serum HBsAg positivity (ever)
   e) Non-therapeutic injection drug use in the 12 calendar months prior to Enrollment
   f) STI or reproductive tract infection (RTI) requiring treatment in the 6 calendar months prior to Enrollment
   g) Post-exposure prophylaxis (PEP) or Pre-exposure prophylaxis (PrEP) within the 6 calendar months prior to Enrollment
   h) Last pregnancy outcome within 90 days or less prior to Enrollment
   i) Gynecologic or genital procedure (e.g., tubal ligation, dilation and curettage) within the 42 days prior 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, provided that all other inclusion/exclusion criteria are met.

   j) Participation in any other research study involving drugs, medical devices or vaginal products 42 days or less prior to Enrollment
   k) Anticipated IUD replacement within the next 3 months or an IUD inserted 42 days or less prior to Enrollment

l) Participant report at Screening and/or Enrollment intention of becoming pregnant in the next 3 months
m) Currently breastfeeding at the time of Screening and/or Enrollment
n) History of bleeding problems (Participants in the biopsy subset only)

2) Laboratory abnormalities at Screening greater than or equal to a Grade 2*:

a) Aspartate aminotransferase (AST) or alanine transaminase (ALT)
b) Hemoglobin
c) Platelet count
d) Serum creatinine

Otherwise eligible participants with an exclusionary test result(s) listed above may be re-tested during the screening process. If a participant is re-tested and a non-exclusionary result is documented within the 42 days of providing informed consent, the participant may be enrolled.

3) Urinary tract infection (UTI) at Screening and/or Enrollment

Note: Otherwise eligible participants diagnosed with UTI during Screening will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 42 days of obtaining informed consent, the participant may be enrolled.

4) Pelvic inflammatory disease or an STI or RTI requiring treatment per current WHO guidelines at Screening and/or Enrollment

5) Clinically apparent Grade 2 or higher pelvic** and/or rectal*** examination finding (observed by study staff) at Screening and/or Enrollment

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

Note: Otherwise eligible participants with exclusionary pelvic and/or rectal examination findings may be enrolled/randomized after the findings have improved to a non-exclusionary severity grading or resolved. If improvement to a non-exclusionary grade or resolution is documented within 42 days of providing informed consent, the participant may be enrolled.

6) 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

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

** per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009), Addendum 1 Female Genital Grading Table for Use in Microbicide Studies

*** per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009), Addendum 3 Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012).

5.4 Co-enrollment Guidelines

As indicated in Section 5.3, participants should not take part in other research studies involving drugs, medical devices, or vaginal or rectal products after the Screening Visit and while taking part in MTN-014. Participation in the following types of studies may be allowed at the discretion of the IoR/designee:

- Participants may take part in studies approved by MTN-014 Protocol Chair and/or Co-Chair

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-014, the IoR/designee will consult the PSRT regarding ongoing product use and other potential safety considerations associated with co-enrollment.

6 STUDY PRODUCT

6.1 Regimen

Each participant will be randomized to one of two administration sequences of TVF RG 1% gel:

Table 1: Study Product Regimen

	N	Period 1: 2 Weeks	Washout: ~6 Weeks	Period 2: 2 Weeks	Dose and Frequency
Sequence A	14	Vaginal		Rectal	Entire contents of a single applicator will be inserted daily
Sequence B	14	Rectal		Vaginal	Entire contents of a single applicator will be inserted daily

6.2 Administration

Clinic staff will attempt to observe each administration of study gel. Participants will be instructed to present to the clinic daily for each 14-day period for direct observed dosing (DOD). Administration of study product will be performed either by participants or by study staff, depending upon site and/or participant preference. If a participant is not able to attend a clinic visit, the participant will be instructed to administer a dose at home at approximately the same time of day as all other daily doses, unless the next dose is due within 6 hours. If the next dose is due within 6 hours, the dose will be skipped and the next dose will be administered as originally scheduled. Participants will receive two pre-filled applicators of TFV RG 1% gel at Visit 2 (Enrollment Visit) and Visit 18 (Initiate Period 2 Visit) in the event that they cannot attend their clinic visit.

Participants will be instructed to insert one dose (the entire contents of one applicator) into the vagina or rectum depending upon their randomization sequence only on the day(s) they are unable to attend the clinic. Study staff will instruct participants in the proper method of study product administration and storage.

6.3 Formulation

The TFV RG 1% gel (weight/weight) is a transparent gel formulation of tenofovir (PMPA, 9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate), formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, hydroxyethylcellulose, and pH adjusted to 4-5. The TFV RG 1% gel has a lower glycerin content than the vaginal formulation and a significantly reduced osmolality (approximately 850 versus approximately 3000 mmol/kg). Compared with the vaginal formulation, the TFV RG 1% gel contains an increased concentration of HEC (not considered significant) due to a lower viscosity caused by the reduced glycerin. The TFV RG 1% gel will be filled into applicators to form pre-filled, single-use applicators. Each pre-filled applicator will contain a dose of approximately 4 grams (equal to 4 mL) of TFV RG 1% gel for delivery. The TFV RG 1% gel must be stored at controlled room temperature, 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 Supply

CONRAD (Arlington, VA, USA) will supply the TFV RG 1% gel. Under direction from CONRAD, DPT Laboratories LTD (San Antonio, TX) which is a contract manufacturing facility, will manufacture the TVF RG 1% gel and analyze/release the gel under cGMP.

6.4.2 Accountability

The Clinical Research Site (CRS) Pharmacist of Record (PoR) is required to maintain complete records of the study product received and subsequently dispensed.

6.4.3 Study Product Dispensing

Following receipt of a written prescription from an authorized prescriber, one pre-filled applicator of study product (TFV RG 1% gel) will be dispensed to enrolled study participants or to study staff at each study product administration visit for DOD. An authorized prescriber includes the IoR or a licensed clinician directly responsible to the IoR as noted on the United States (US) Food and Drug Administration (FDA) 1572 Form.

Participants will receive two pre-filled applicators of TFV RG 1% gel for at home use for each study period. These doses will be dispensed at both Visit 2, the beginning of Period 1, and at Visit 18, the beginning of Period 2. Details regarding the dispensation

of additional doses will be provided in the MTN-014 Study Specific Procedures (SSP) Manual available at www.mtnstopshiv.org. No study product will be dispensed during the study washout phase.

6.4.4 Ancillary Study Supplies

All participants will be offered study-provided male condoms, panty liners and lubricant. The condoms, panty liners and lubricant for applicator administration will be dispensed by the clinic staff and made available in the clinic.

6.4.5 Retrieval of Unused Study Product

Study participants will be instructed to return all unused study product to the site at Visit 15 (the last Study Product Administration Visit of Period 1) and Visit 31 (the last Study Product Administration Visit of Period 2).

As per Section 9.3, study product use for a participant may be temporarily held or permanently discontinued. Study product must be retrieved (optimally within 24 hours) and returned to the study site pharmacy when study product use is permanently discontinued or if product is instructed to be held for more than 7 days.

Study product retrieval will occur by the participant returning the product to study staff within the specified timeframe. Attempts by study staff to retrieve unused study product from the participant must be documented.

It is not necessary to retrieve unused study product from participants for whom study product use is being temporarily held for less than 7 days. However, study product(s) may be retrieved from such participants, to protect their safety, if there is concern that the participant may not comply with clinic staff instructions to refrain from study product use for the duration of the temporary hold. For all study product holds where study product is being permanently discontinued or temporarily held for more than 7 days, if the study product(s) are not retrieved within 7 days the MTN-014 PSRT must be informed.

For each participant, unused study product not previously returned must be retrieved at the Period 2 End/Final Clinic Visit (Visit 32). If the participant does not bring her remaining unused study product to the Final Clinic Visit, study staff must arrange to retrieve the unused study product within 7 days. If the study product(s) are not retrieved within that timeframe, the MTN-014 PSRT must be informed.

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

6.5 Study Product Dosing Assessment and Study Product Adherence Counseling

Data on adherence to study gel will be recorded at Period 1 End and at Period 2 End via case report form (CRF).

Product adherence counseling will be provided to study participants upon enrollment into the study, and every visit when study product is dispensed thereafter to help ensure high rates of study product use. Counseling will be provided in accordance with standard study methods. Participants will be counseled to return to the clinic daily during the product use periods for directly observed gel administration. Participant-centered strategies to ensure the use and availability of the study product both in the home and away from home will also be provided. Counseling also will include reminders to contact study staff with questions about study product use.

For participants who have adherence problems and/or issues presenting to the clinic for the administration of study product, every effort will be made to identify adherence strategies to increase their rates of study product use and attendance to daily clinic visits throughout the course of the study.

6.6 Concomitant Medications

With the exception of those not permitted under inclusion and exclusion criteria, and listed below, concomitant medications will be permitted. Throughout the course of the study, all concomitant medications, including those used to treat AEs, will be recorded on forms designed for that purpose. Prescription medications, over-the-counter preparations, vitamins and nutritional supplements, and herbal preparations all will be recorded as concomitant medications.

6.7 Prohibited Medications and Practices

All participants will be counseled to avoid the use of non-study vaginal or rectal products, for the duration of the product use periods and 24 hours prior to Period Initiation Visits and Period End Visits. Concomitant use of prohibited non-study vaginal products or other devices including, but not limited to: spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), vaginal/rectal douches, enemas, non-study approved lubricants, sex toys (vibrators, dildos, etc.), and tampons will be assessed. These products will be recorded on forms designed for that purpose. Participants who report use of prohibited products during study product use periods will be counseled regarding the use of alternative methods. Condoms provided by study staff will not be coated with any type of spermicide.

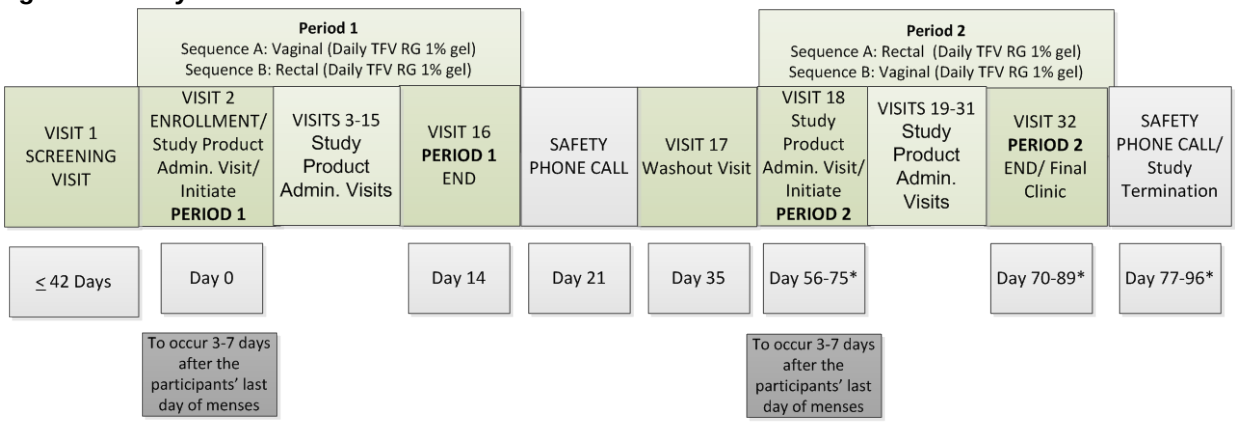
Furthermore, a subset of participants will also be counseled not to use NSAIDs, aspirin and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours prior to and following mucosal biopsy collection. Should a participant report the

use of such drugs within 72 hours prior to a biopsy visit, collection of biopsies at that visit would be performed at IoR discretion. Participants are to abstain from inserting any non-study products into their vagina or rectum for 72 hours prior to and following the collection of biopsies. Further, they are to abstain from vaginal and rectal intercourse for 72 hours prior to and following the collection of biopsies. Participants will be appropriately counseled regarding the potential risks associated with biopsy collection and documentation of the decision process will be included in the participants' study documents. Rapid PSRT consultation can be requested at IoR discretion, if needed.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is provided in Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites are provided in the MTN-014 Study Specific Procedures (SSP) Manual available at www.mtnstopshiv.org.

Figure 2: Study Visit Schedule



* Visit schedule will vary based upon participants' menses.

7.1 Screening Visit

A Screening Visit may take place up to 42 days prior to the Visit 2: Enrollment/Study Product Admin. Visit/Initiate Period 1 Visit. Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed consent will be obtained before any study procedures are initiated. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined.

Table 2: Screening Visit

Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent • Assign participant identification (PTID) • Collect locator information • Collect demographic information • Eligibility assessment • Reimbursement • Schedule next visit*
Behavioral/Counseling		• Provide counseling o HIV/STI risk reduction o Male condom o HIV pre-and post-test o Biopsy procedure▪
Clinical		• Obtain medical history • Obtain menstrual history • Provide contraceptive counseling • Obtain concomitant medications • Perform physical examination • Perform pelvic examination • Perform rectal examination • Disclosure of available test results • Treat for UTI/RTI/sexually transmitted infection (STI) or refer*
Laboratory	**Urine**	• Collect urine for: o Qualitative hCG o Dipstick UA* o Urine culture*
	Blood	• Collect blood for: o Chemistries o CBC with platelets o HIV-1 serology o Syphilis serology
	Pelvic Samples	• Collect pelvic specimens for: o Vaginal nucleic acid amplification test (NAAT) for Neisseria gonorrhoeae (GC)/ Chlamydia trachomatis (CT) o Vaginal swab for rapid Trichomonas test o Vaginal biopsy for mucosal gene expression microarray▪ o Vaginal fluid for KOH wet mount for candidiasis* o Vaginal fluid for Saline wet mount for bacterial vaginosis (BV)* o Vaginal fluid for pH* o Cervical specimen for Pap smear*
	Rectal Samples	• Collect rectal biopsy for mucosal gene expression microarray▪
Study Product Supply		• Provide study condoms*

* If indicated, ▪To be collected/performed during the screening process at the US site on all women who have not already had their screening terminated due to ineligibility (samples to be collected are for gene expression only).

7.2 Visit 2: Enrollment (Day 0)/ Study Product Administration Visit/ Initiate Period 1

Once ineligibility is determined at Visit 2: Enrollment (Day 0)/ Study Product Administration Visit/ Initiate Period 1 all procedures will discontinue.

Table 3: Enrollment (Day 0)/ Study Product Administration Visit/ Initiate Period 1

Visit 2: Enrollment Visit/ Study Product Administration Visit/ Initiate Period 1		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Confirm eligibility • Randomization • Reimbursement • Schedule next visit
Behavioral/Counseling		• Provide counseling o HIV/STI risk reduction o Male condom* o HIV pre-and post-test o Protocol adherence o Product use instructions and adherence
Clinical		• Review/update medical history • Review/update menstrual history • Provide contraceptive counseling* • Review/update concomitant medications • Perform targeted physical examination • Perform pelvic examination • Perform rectal examination • Vaginal/Rectal dose observation • Disclosure of available test results • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o Qualitative hCG o Dipstick UA* o Urine culture* o Urine NAAT for GC/CT*
	Blood	• Collect blood for: o HIV-1 serology o Plasma archive
	Pelvic Samples	• Collect pelvic specimens for: o Vaginal swab for biomarkers o Cervical swab for biomarkers o CVL for PD and biomarkers o Gram stain o Vaginal fluid for pH o Vaginal swab for rapid Trichomonas test* o Vaginal fluid for KOH wet mount for candidiasis* o Vaginal fluid for saline wet mount for BV*
	Rectal Samples	• Collect specimens for: o Rectal fluid for PD and biomarkers
Study Product Supply		• Provision of study product • Provision of panty liners*

	• Provision of lubricant* • Provision of study condoms*

* If indicated

7.3 Visits 3-15: Study Product Administration Visits

Table 4: Visits 3-15: Study Product Administration Visits

Visits 3-15: Study Product Administration Visits	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Reimbursement • Schedule next visit*
Clinical	• Collect AEs • Review/update concomitant medications • Vaginal/Rectal dose observation • Treat for UTIs/RTIs/STIs or refer*
Study Product Supply	• Provide study product • Provision of panty liners* • Provision of lubricant* • Provision of condoms* • Collect unused study product▲

* If indicated, ▲ to be performed at the final study product administration visit

7.4 Visit 16: Period 1 End (Day 14)

Table 5: Visit 16: Period 1 End (Day 14)

Visit 16: Period 1 End (Day 14)	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Schedule next study visit and follow-up safety phone call • Reimbursement
Behavioral/Counseling	• Complete Study Product Dosing Assessment • Provide counseling o HIV/STI risk reduction o Male condom* o HIV pre-and post-test* o Protocol adherence o Biopsy procedure▪
Clinical	• Review/update medical history • Review/update menstrual history • Provide contraceptive counseling* • Review/update concomitant medications • Perform targeted physical examination • Perform pelvic examination • Perform rectal examination • Disclosure of available test results • Record/update AEs • Treat for UTIs/RTIs/STIs or refer*

Laboratory	**Urine**	• Collect urine for: o Qualitative hCG o Dipstick UA* o Urine culture* o Urine NAAT for GC/CT*
	Blood	• Collect blood for: o PK o HIV-1 serology*
	Pelvic Samples	• Collect pelvic specimens for: o Vaginal swab for biomarkers o Cervical swab for biomarkers o Vaginal fluid for PK o CVL for PK,PD,& biomarkers o Cervical cytobrush for PK o Gram stain o Vaginal pH o Vaginal biopsies for PK and mucosal gene expression microarray▪ o Vaginal swab for rapid Trichomonas test* o Vaginal fluid for KOH wet mount for candidiasis* o Vaginal fluid for saline wet mount for BV*
	Rectal Samples	• Collect rectal specimens for: o Rectal fluid for PK, PD and biomarkers o Rectal biopsies for PK and mucosal gene expression microarray▪
Study Product Supply		• Collect unused study product* • Provide study condoms*

* If indicated, ▪ All participants at the US site only. See Section 7.14 for additional details.

7.5 Visit 17: Washout (Day 35)

Table 6: Visit 17: Washout (Day 35)

Visit 17- Washout (Day 35)		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Reimbursement • Schedule next visit
Behavioral/Counseling		• Provide counseling o HIV/STI risk reduction o Male condom* o HIV pre-and post-test* o Protocol adherence
Clinical		• Review/update medical history • Review/update menstrual history • Review/update concomitant medications • Record/update AEs • Provide contraceptive counseling* • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o Qualitative hCG
	Blood	• Collect blood for: o HIV-1 serology*

Study Product Supply	• Provide study condoms*

* If indicated

7.6 Visit 18: Study Product Administration/Initiate Period 2 (Day 56-75*)

* Visit schedule will vary based upon participants' menses.

The PSRT must be consulted regarding progression into the next dosing period prior to the initiation of study product for Period 2, for any participant who has unresolved abdominal, genital, or anorectal AEs of any Grade or unresolved Grade 3 or 4 AEs regardless of organ system.

Table 7: Visit 18 Study Product Administration/Initiate Period 2 (Day 56-75)

Visit 18: Study Product Administration/Initiate Period 2 (Day 56-75*)		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Reimbursement • Schedule next visit
Behavioral/Counseling		• Provide counseling o HIV/STI risk reduction o Male condom* o HIV pre- and post-test counseling o Protocol adherence o Product use instructions and adherence
Clinical		• Review/update medical history • Review/update menstrual history • Review/update concomitant medications • Provide contraceptive counseling* • Perform targeted physical examination • Perform pelvic examination • Perform rectal examination • Vaginal/Rectal dose observation • Disclosure of available test results • Record/update AEs • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o Qualitative hCG o Dipstick UA* o Urine culture* o Urine NAAT for GC/CT*
	Blood	• Collect blood for: o PK o HIV serology
	Pelvic Samples	• Collect pelvic specimens for: o Vaginal swab for biomarkers o Cervical swab for biomarkers o Vaginal fluid for PK o CVL for PK, PD, and biomarkers o Gram stain o Vaginal pH o Vaginal swab for rapid Trichomonas test* o Vaginal fluid for KOH wet mount for candidiasis* o Vaginal fluid for saline wet mount for BV*

	Rectal Samples	• Collect rectal specimens for: o Rectal fluid for PK, PD and biomarkers
Study Product Supply		• Provision of study product • Provision of panty liners* • Provision of condoms* • Provision of lubricant*

* If indicated

7.7 Visits 19-31: Study Product Administration Visits

Table 8: Visits 19-31: Study Product Administration Visits

Visits 19-31: Study Product Administration Visits	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Reimbursement • Schedule next visit*
Clinical	• Collect AEs • Review/update concomitant medications • Vaginal/Rectal dose observation • Treat for UTIs/RTIs/STIs or refer*
Study Product Supply	• Provide study product • Provision of panty liners* • Provision of lubricant* • Provision of condoms* • Collect unused study product▲

* If indicated, ▲ to be performed at the final study product administration visit

7.8 Visit 32: Period 2 End/Final Clinic Visit (Day 70-89*)

* Visit schedule will vary based upon participants' menses.

Table 9: Visit 32: Period 2 End/Final Clinic Visit (Day 70-89*)

Visit 32: Period 2 End/Final Clinic Visit (Day 70-89*)	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Reimbursement • Schedule next follow-up safety phone call
Behavioral/Counseling	• Complete Study Product Dosing Assessment • Provide counseling o HIV/STI risk reduction o Male condom* o HIV pre-and post-test o Biopsy procedure▪
Clinical	• Review/update medical history • Review/update menstrual history • Review/update concomitant medications • Provide contraceptive counseling* • Perform targeted physical examination • Perform pelvic examination

		• Perform rectal examination • Disclosure of available test results • Record/update AEs • Treat for UTIs/RTIs/STIs or refer*
Laboratory	**Urine**	• Collect urine for: o Qualitative hCG o Dipstick UA* o Urine culture* o Urine NAAT for GC/CT*
	Blood	• Collect blood for: o PK o Chemistries* o CBC with platelets* o HIV-1 serology
	Pelvic Samples	• Collect pelvic specimens for: o Vaginal swab for biomarkers o Cervical swab for biomarkers o Vaginal fluid for PK o CVL for PK, PD, and biomarkers o Cervical cytobrush for PK o Vaginal biopsies for PK and mucosal gene expression microarray▪ o Gram stain o Vaginal pH o Vaginal swab for rapid Trichomonas test* o Vaginal fluid for KOH wet mount for candidiasis* o Vaginal fluid for saline wet mount for BV*
	Rectal Samples	• Collect rectal specimens for: o Rectal fluid for PK, PD and biomarkers o Rectal biopsies for PK and mucosal gene expression microarray▪
Study Product Supply		• Provision of condoms* • Collect unused study product*

* If indicated, ▪ All participants at the US site only. See Section 7.14 for additional details.

7.9 Safety Phone Calls

Approximately one week following Visit 16 and Visit 32, study staff will contact participants to inquire about AEs that they might have experienced as a result of the study product or procedures performed. The phone call that follows Visit 32 is Study Termination.

Table 10: Safety Phone Calls

Safety Phone Calls	
Component	**Procedures**
Administrative and Regulatory	• Reimbursement~ • Locator information • Schedule interim visit*
Clinical	• Record/update AEs

~ Sites to reference SOPs regarding participant reimbursement, * If indicated

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

7.10.1 Participants Who Become Infected with HIV-1

If a participant becomes infected with HIV-1 after the Enrollment Visit, she will be referred to local care and treatment services and may return to the research clinic for additional counseling and other support services, as needed. Continued study participation would be of no added benefit, thus follow-up visits will be discontinued and the participant will be considered terminated from the study. Participants who seroconvert after randomization may be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), as clinically indicated per discussion between IoR and NL. Please reference the MTN-014 SSP Manual for additional details (www.mtnstopshiv.org).

Participants who become infected with HIV-1 while on study product may be offered enrollment in MTN-015, the MTN Seroconverter Study, provided their study site is taking part in MTN-015. Participants are offered enrollment in MTN-015 (www.mtnstopshiv.org) at the visit when seroconversion confirmation test results are discussed with the participant.

7.10.2 Participants Who Become Pregnant

If a participant becomes pregnant, she will be referred to local health care services and may return to the research clinic for additional counseling, as needed. Continued study participation would be of no added benefit to the participant, thus follow-up visits and procedures will be discontinued and the participant will be considered terminated from the study.

Participants who become pregnant while on study product may be offered enrollment in MTN-016 (www.mtnstopshiv.org), provided their study site is taking part in MTN-016.

For additional details regarding obtaining pregnancy outcome, please reference the MTN-014 SSP (www.mtnstopshiv.org).

7.10.3 Participants Who Permanently Discontinue for Other Reasons

For participants who permanently discontinue study product use for any other reason other than HIV seroconversion or pregnancy, site investigators may, after consultation with the PSRT, decide to discontinue study follow-up visits and procedures. However, participants who permanently discontinue study product use due to AE must continue to be followed until the resolution or stabilization of the AE is documented.

In the event site study follow-up visits and procedures are continued, all protocol-specified study visits and procedures will continue except the following:

- Study Product Administration Visits/Procedures
- Provision of study product, instructions and adherence counseling
- PK/PD/mucosal gene expression microarray specimen collection
- Pelvic exams*
- Rectal exams*

*Unless required for AE follow-up

7.11 Participants Who Temporarily Hold Study Product

Voluntarily or under IoR Discretion
All protocol-specified study visits and procedures will continue except the following:

- Study Product Administration Visits/Procedures
- Provision of study product, instructions and adherence counseling
- PK/PD/mucosal gene expression microarray specimen collection
- Pelvic exams*
- Rectal exams*

*Unless required for AE follow-up

These study procedures will be omitted at subsequent visits that occur during the time participants are off study product. Completion of these procedures will resume if and when the participant resumes study product use.

7.12 Interim Visits

Interim contacts and visits may be performed at any time during the study. Interim study procedures will be performed as clinically indicated. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.

7.13 Pharmacokinetics/Pharmacodynamics

All study participants will have the following samples collected to assess PK and PD.

Table 11: PK/PD Specimen Collection Schedule

Visit	Specimens Collected for PK	Specimens Collected for PD
Visit 2: Enrollment/ Study Product Admin. Visit/ Initiate Period 1 (Day 0)		• Rectal fluid • CVL
Visit 16: Period 1 End	• Blood • Vaginal fluid • Rectal fluid • CVL • Cervical cytobrush	• Rectal fluid • CVL
Visit 18: Study Product Admin. Visit/Initiate Period 2	• Blood • Vaginal fluid • Rectal fluid • CVL	• Rectal fluid • CVL
Visit 32: Period 2 End	• Blood • Vaginal fluid • Rectal fluid • CVL • Cervical cytobrush	• Rectal fluid • CVL

7.14 Intensive Pharmacokinetics and Mucosal Gene Expression Microarray Subset

Participants at a single US site must agree to the collection of biopsies in order to take part in MTN-014. All women at the US site, provided that they are not found to be ineligible for other reasons, will provide a vaginal and rectal biopsy. It is anticipated that all US participants (approximately 14 participants) will be enrolled into the study and take part in the biopsy subset. Details regarding the quantity and timing of mucosal sample collection for intensive PK and mucosal gene expression microarray for this subset are described in Table 12.

Biopsy procedural counseling will precede each biopsy collection. Counseling will include, but not be limited to, the following information: Participants will be asked to refrain from the use of NSAIDs, aspirin and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours prior to and following mucosal biopsy collection. During the counseling session participants will be instructed to abstain from inserting any non-study product into the vagina or rectum, including abstaining from sexual activity, for 72 hours before and after the collection of samples. All heterosexually-active participants will be reminded of the importance of using male condoms with each sex act, as all biopsy subset participants will be at increased risk of HIV/STI transmission following biopsy collection. In the event that a participant reports prohibited medication/practices the site should reference Section 6.7.

It is important to note that because the half-life is so long in both vaginal and rectal tissue (2 days) a delay of several hours between vaginal sampling and rectal sampling will result in negligible drug clearance in this interval, thus the sampling sequence (vaginal vs. rectal) can be determined at the clinician's discretion.

At the time of biopsy collection, if a pelvic or rectal exam finding is suggestive of cervicitis, vaginitis, proctitis or another inflammatory condition, the IoR will use discretion with regard to proceeding with the biopsy collection.

Detailed instructions are provided in the MTN-014 SSP Manual available at www.mtnstopshiv.org.

Table 12: Intensive Pharmacokinetics and Mucosal Gene Expression Microarray Subset Sample Collection

Visit	Specimens Collected for PK	Specimens Collected for Microarray
Visit 1: Screening		• 1 Vaginal Biopsy ▪ • 1 Rectal Biopsy ▪
Visit 16: Period 1 End	• 2 Vaginal Biopsies • 4 Rectal Biopsies	• 1 Vaginal Biopsy • 2 Rectal Biopsies
Visit 32: Period 2 End	• 2 Vaginal Biopsies • 4 Rectal Biopsies	• 1 Vaginal Biopsy • 2 Rectal Biopsies

▪To be collected during the screening process at the US site on all women who have not already had their screening terminated due to ineligibility.

7.15 Clinical Evaluations and Procedures

Physical Examination

The physical examination will include the following assessments:

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

- Skin*
- Neurological*

*may be omitted after the Screening Visit

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

Pelvic Examination and Specimen Collection

Pelvic examinations will be conducted per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at http://www.conrad.org/publications-13.html. The required sequence of procedures and specimen collection to be performed during the pelvic exam will be specified in the MTN-014 SSP Manual.

Rectal Examination and Specimen Collection

Rectal examinations and specimen collection will be conducted per guidelines provided in the SSP. The required sequence of procedures and specimen collection to be performed during the rectal exam will be specified in the MTN-014 SSP.

7.16 Laboratory Evaluations

Local Laboratory

- Qualitative hCG
- Dipstick UA (protein, blood, nitrites and leukocyte esterase)
- Urine culture (may omit if culture not standard of care for UTI diagnosis as per site standard SOP)
- Vaginal NAAT for GC/CT
- Urine NAAT for GC/CT
- Chemistries
- CBC with platelets
- HIV-1 serology, including plasma for confirmation
- Syphilis serology
- Rapid Trichomonas test
- KOH wet mount for candidiasis
- Saline wet mount for BV
- Vaginal pH
- Pap smear

Network Laboratory (NL)

- Plasma archive
- Tenofovir drug levels (Pharmacokinetics-PK)
- Antiviral activity (Pharmacodynamics-PD)

- Confirmation of HIV-1 serology for seroconversion, as required per algorithm in Appendix II
- Biomarkers
- Gram stain
- Mucosal gene expression microarray

7.17 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical laboratory practice, in accordance with current DAIDS Laboratory Requirements, MTN-014 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.

7.18 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)

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

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

Site IoRs 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 and CONRAD Medical Officers, Protocol Safety Physician, and SCHARP Clinical Affairs Safety Associate 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.

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. 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 can 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. If at any time a decision is made to discontinue enrollment and/or study product use in all participants,

CONRAD will notify the US FDA and the CRS Principal Investigator will notify the responsible IRB/EC 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 administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition is applied to all study groups, and is applied to all groups beginning at the time of enrollment (i.e., randomization) to the final study visit. The term "investigational product" for this study refers to TFV RG 1% gel, and the study gel applicator.

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 the appropriate AE Log CRF all Grade 2 and higher AEs and Grade 1 Genitourinary and Rectal AEs as reported by or observed in enrolled study participants, regardless of presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), as well as Addendum 1, Female Genital Grading Table for Use in Microbicide Studies and Addendum 3, Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012), except that asymptomatic BV and asymptomatic candidiasis will not be reportable AEs. In cases where a genital AE is covered in both tables, either the Female Genital Grading Table or the Rectal Grading Table (Clarification dated May 2012) mentioned above will be the scales utilized.

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 any AEs that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
  Note: Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event. Thus, hospitalization in the absence of an AE is not regarded as an AE, and is not subject to expedited reporting. The following are examples of hospitalization that are not considered to be AEs:
    - Protocol-specified admission (e.g., for procedure required by study protocol)
    - Admission for treatment of target disease of the study, or for pre-existing condition (unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator)
    - Diagnostic admission (e.g., for a work-up of an existing condition such as persistent pretreatment lab abnormality)
    - Administrative admission (e.g., for annual physical)
    - Social admission (e.g., placement for lack of place to sleep)
    - Elective admission (e.g., for elective surgery)

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

8.3.3 Adverse Event Relationship to Study Product

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

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

8.4 Expedited Adverse Event Reporting Requirements

8.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited adverse event (EAE) reporting are outlined in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS, which is available on the Regulatory Support Center (RSC) website at http://rsc.tech-res.com/safetyandpharmacovigilance/. For each study participant, EAE reporting will be undertaken throughout the scheduled duration of follow-up, i.e., from the time of random assignment through study termination.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs 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 EAEs 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 prepare the draft safety reports and send them to the CONRAD and DAIDS MO 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 US 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 Version 2.0 of the DAIDS Manual for Expedited Reporting of Adverse Events to DAIDS, will be used for this study
- The study agents for which expedited reporting are required are:
    - TFV RG 1% gel
    - Study gel applicator

8.4.3 Grading Severity of Events

The grading of severity of events and the reporting period will be the same as for all AEs, as described in Section 8.3.1. The most current Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 December 2004 (Clarification dated August 2009), Addendum 1, Female Genital Grading Table for Use in Microbicide Studies, and Addendum 3, Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012) will be used and are available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

8.4.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study begins once the participant is randomized and continues up through the participant's Study Termination

- 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 Manual for Expedited Reporting of Adverse Events to DAIDS will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information)

8.5 Pregnancy and Pregnancy Outcomes

Pregnant women are excluded from this study.

Pregnancy-related data will be collected using 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 AE in the pregnant participant that meets expedited reporting criteria or the pregnancy results in a congenital anomaly meeting ICH guidelines for expedited reporting.

8.6 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the PSRT and responsible site IRB/EC according to their individual requirements. In the event that a participant reports social harm, every effort is made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Each site will provide such care and counseling in accordance with standardized guidance provided in the MTN-014 SSP Manual. While maintaining participant confidentiality, study sites may engage their community advisory boards (CABs) in exploring the social context surrounding instances of social harm.

8.7 Regulatory Requirements

Information on all reported AEs will be included in reports to the US 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 IRB/EC in accordance with IRB/EC requirements.

9 CLINICAL MANAGEMENT

Guidelines for clinical management and temporary product hold/permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to hold study product temporarily at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. 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 in this study.

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

- Acquisition of HIV-1 infection; study product will be permanently discontinued upon recognition of the first reactive HIV-1 test
- Pregnancy (permanent discontinuation)
- Breastfeeding (permanent discontinuation)
- Report of use of post-exposure prophylaxis (PEP) or Pre-exposure prophylaxis (PrEP) (permanent discontinuation)

- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee.

    - The IoR/designee must consult the PSRT on all temporary product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation.
    - If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time.

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

All AEs are 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), and Addendum 1, Female Genital Table for Use in Microbicide Studies and Addendum 3, Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012).

Grade 1 or 2

In general, a participant who develops a Grade 1 or 2 AE regardless of relationship to study product that is not specifically addressed below may continue product use. If the IoR opts to temporarily hold study product, the PSRT must be notified.

Follow-up testing for Grade 2 laboratory test results should be performed at scheduled study visits, at a minimum, until resolution or stabilization has been documented. More frequent testing may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR/designee.

Grade 3 and 4

A participant who develops a Grade 3 or a Grade 4 AE 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. If, in consultation with the PSRT, product use is resumed and the same AE recurs at the same grade level at any time during the study, study product must then be permanently discontinued.

9.5 Genital Sexually Transmitted Infection/Reproductive Tract Infection

The IoR/designee should manage STI/RTI per current WHO guidelines, available at http://www.who.int/en/. Observed single oral dose should be provided whenever possible.

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

9.6 HIV-1 Infection

Participants identified as infected with HIV are managed or referred for management according to the local standard of care. Participants will be offered additional counseling in the clinic, if needed. If a participant has a positive test for HIV-1, study product will be permanently discontinued by the IoR/designee. Because continued study participation would be of no added benefit to participants, all follow-up visits will be discontinued and participants will be considered terminated from the study. These participants are also offered participation in MTN-015, the MTN Seroconverter Study, provided their site is participating in MTN-015, which also includes provisions for the clinical management and/or referral of participants infected with HIV. Sites will not be responsible for paying for HIV-related care.

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

Results of study laboratory testing may be helpful in clinical management; these results are provided to the participant and her medical provider as soon as they are available.

9.7 Pregnancy

All study participants are required to be using an effective method of contraception according to Section 5.2 at Visit 2: Enrollment/Study Product Admin Visit/Initiate Period 1 (Day 0). Study staff will provide contraceptive counseling to enrolled participants as needed throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery. Study staff also will provide participants with condoms and counseling on use of condoms ideally during every sex act during study participation.

Pregnancy testing is performed at all study visits and may be performed as indicated at interim visits. In addition, participants are 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 the Final Clinic Visit 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 are reported on relevant CRFs; outcomes meeting criteria for EAE reporting also are reported on EAE forms.

A participant who becomes pregnant during the course of the study will have study product discontinued and will not be followed, as per Section 7.10.2.

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

For additional details regarding obtaining pregnancy outcome, please reference the MTN-014 SSP Manual (www.msnstopshiv.org).

9.8 Criteria for Voluntary 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 US FDA and Office for Human Research Protections (OHRP), or site IRB/EC 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.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and General design

This is a two-period, two treatment, open label, crossover study to evaluate the local pharmacokinetics of tenofovir reduced-glycerin 1% gel after 2 weeks of rectal and vaginal use. The sequence of rectal use and vaginal use will be randomly assigned. There is a minimum 6-week washout period between the two 2-week use periods.

10.2 Study Endpoints

10.2.1 Primary Study Endpoints

Consistent with the primary study objectives, the following primary endpoints will be assessed:

The pharmacokinetic endpoints are drug levels in:

- Blood
- Vaginal fluid
- Cervical cytobrush
- Rectal fluid
- Cervicovaginal lavage
- Vaginal tissue
- Rectal tissue

Note: All US participants (approximately 14 total) will supply vaginal and rectal tissue samples. See Section 7.14 for additional details.

10.2.2 Secondary Study Endpoints

Consistent with the secondary study objective to assess safety, the following safety endpoint will be assessed:

- Adverse events Grade 2 or higher as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009), Addendum 1, Female Genital Grading Table for Use in Microbicide Studies, and Addendum 3, Rectal Grading Table for Use in Microbicide Studies (Clarification dated May 2012)

10.2.3 Exploratory Study Endpoints

Consistent with the exploratory study objectives, the following exploratory endpoints will be assessed:

- Inhibition of HIV by drug in rectal and genital fluids
- Changes in pH, microflora, biomarkers and gene expression

10.3 Sample size and power

The sample size and power calculation for a crossover design can start from two-arm, equal size comparison assuming the independence, then adjust this resulted sample

size by intro-women correlation in the crossover design. The sample size adjustment can be obtained by this formula:

N'=N(1-rho)/2

Where N' is the sample size for a crossover design, N is total number required for a two independent arm design, and rho is the correlation between drug concentrations after two routes of gel use within the same women.

Based on the MTN-001 and MTN-006 data, the TFV concentrations in blood, vaginal fluid, rectal fluid, and tissue biopsy are quite variable. Take vaginal tissue TFV in MTN 001 for example, the mean concentration is 218 ng/mg and the standard deviation is 280, so the coefficient of variation (CV) is almost 1.4. The CV for the active form TFV-DP is around 1.5. The concentration in the vaginal fluid is more variable with CV reaching as high as 3. Similar level of variability was observed for rectal dosing in MTN 006 (Tissue TFV-DP 1.3, rectal sponge 1.0). We estimate the CV for tissue TFV-DP is around 1.0-1.5, and with improved technology for fluid level of TFV, we estimated its CV around 2.

To compute the power for comparing the concentrations of one compartment under the two routes of gel use, we assume the coefficients of variation vary at 1, 1.5 or 2, and we assume the within-individual correlation ranges from 0.2 to 0.8. For effective sample size 12 or 24 participants who have completed data for both rectal use and vaginal use, we list the power to detect significant difference between the concentrations under two routes in Table 13, when the fold change of concentration is 10. The coefficients of variation remain the same for the concentrations under two routes of use. Because it is expected that the same compartment delivery will result in higher concentration than the cross compartment delivery, we use one-sided type I error in the power computation. The test statistic is one sample test of mean being different from 0, accounting for within-subject correlation.

Table 13 shows the power of detecting 10-fold difference in concentration for a sample size of 12 or 24. The total effective sample size of 24 will provide the following power performance: for less variable drug concentration such as tissue TDF-DP, which will be collected only in half of total effective sample size (12 women at a single US site), suppose its CV is around 1.0-1.5, we have power to detect a 10-fold difference or more; for more variable drug concentration with CV around 2, such as those in rectal or vaginal fluid, we have close to 80% power to detect a 10-fold difference.

Table 13: The power to detect significant difference for crossover design for a sample size 12 or 24

The power to detect significant difference for crossover design for an effective sample size of 12 or 24, the coefficient variation 1.0, 1.5 or 2, within subject correlation 0.2, 0.5, or 0.8, and the actual fold difference is 10. The one sided type I error is set to 0.05.			
CV	Rho	Total sample size	
		12	24
1.0	0.2	0.94	1.0
1.0	0.5	0.95	1.0
1.0	0.8	0.96	1.0
1.5	0.2	0.68	0.91
1.5	0.5	0.70	0.93
1.5	0.8	0.73	0.94
2.0	0.2	0.48	0.73
2.0	0.5	0.50	0.75
2.0	0.8	0.52	0.78

It is important to note that participants may fail to complete both periods. The recently completed MTN-001 trial, which also used a crossover design, has approximately 1/6 participants who did not complete the study crossover periods. The sample size calculation is based upon participants who successfully completed the study and adds additional enrollees to cover the potential for participants who fail to complete the study. To compensate the potential data loss, in the MTN-014 trial four more participants will be enrolled, thus a sample size of 28 is targeted.

10.4 Randomization Procedures

Randomization to the sequence of gel administration will be stratified by site, with equal number of participants recruited for each of the two sites. Within each site, participants will be randomly assigned with the ratio 1:1 to one of two study product use sequences: rectal use followed by vaginal use or vaginal use followed by rectal use. The randomized assignments will be in blocks to keep the balance of equal allocation. The SDMC will provide each study site with a series of numbered, sealed envelopes containing the randomization assignment for each participant. The envelopes will be assigned sequentially by site staff. The MTN Statistical and Data Management Center will coordinate the randomization procedures, which will be specified in the SSP Manual.

10.5 Participant Accrual and Retention

The accrual period is expected to require approximately 10 months. The study will enroll 28 women.

The target retention rate for each study visit is 100%. Therefore, once a participant is enrolled in the study, the study site will make every reasonable effort to retain her for the entire study duration so that she is evaluable and to minimize possible bias associated with loss-to-follow-up. An average overall retention rate of 95% will be targeted at each site.

10.6 Data Analyses

10.6.1 Primary Data Analyses on PK Measures

All participants who have PK data collected will be used in the analysis. The comparison is primarily based on the concentrations of the same compartment delivery and the cross-compartment delivery. For the drug concentration in each compartment under one route of gel use, mean and standard deviation will be computed for each period separately, and for two periods of the same route combined. The skewness of drug concentration values will be assessed and log transformation will be considered if this is the case. The drug concentration in the beginning of the treatment Period 2 will be used to determine if there is a carryover effect from the previous treatment period. If there is no carryover effect, a linear mixed model will be used to account for the crossover design, paired data structure and controlling for period effect. For the tissue concentrations collected in 14 participants in the US site, a signed rank Wilcoxon test will be also conducted. Although no carryover effect would be expected after a minimum 6-week washout period, if that is detected, we will resort to analyzing only the data from the Period 1 as a simple two arm parallel design using statistical methods for independent data.

10.6.2 Secondary Data Analyses on AEs

A list of AEs as defined as secondary endpoints will be tabulated by the route of drug application and the treatment period. The difference of AE rates between different routes of delivery will be assessed by a generalized linear mixed model accounting for the period effect.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents. 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://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Default.aspx)

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

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

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with current DAIDS policies. (http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/qmppolicy.pdf)

12 CLINICAL SITE MONITORING

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

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

- Verify proper storage, dispensing, and accountability of an investigational study product
- 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 form(s), 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 study monitors, study staff, including authorized representatives of the MTN CORE, SDMC, and NL; NIH, NIAID, the US FDA, CONRAD, US Office for Human Research Protections (OHRP), IRB/EC and local IRB/EC and local authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Boards/Ethics Committees

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

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local IRB/EC and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the 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* be reviewed and approved by the DAIDS PRO and sites *will* receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required

documents have been received. Site-specific ICF(s) *will not* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

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

13.3 Study Coordination

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 Trial Agreement (CTA) executed by NIAID and CONRAD.

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

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

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

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

Participants at sites requiring partner notification in response to diagnosed STI or HIV infection could have problems in their relationships with their sexual partners. Participants also could have problems in their partner relationships associated with use or attempted use of study gel.

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

Vaginal and Rectal Biopsies Collection

For a subset of participants, vaginal and rectal biopsies carry the risk of discomfort or pain during the procedure and for a few hours afterwards. Participants may have mild vaginal and rectal spotting (bleeding) for one or two days. Participants may also be at increased risk for STIs and HIV acquisition, if exposed. Participants will be instructed to refrain from sexual intercourse and counseled not to use NSAIDs, aspirin and/or other drugs that are associated with the increased likelihood for 3 days before and after the collection of the biopsy. If participants engage in sexual intercourse before the biopsy has healed they may experience some temporary discomfort. There is a small risk of infection and heavier bleeding. Participants will be encouraged to call the clinic to report any AE after the collection, especially 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.

The biopsies are painless and heal quickly within 3 to 5 days. On extremely rare occasions, biopsies may lead to pain, bleeding or perforation of the gastrointestinal tract, or infection. Perforation occurs approximately less than once out of every 1,000 procedures. If this extremely rare complication occurs, antibiotics and surgery to repair the tear may be necessary.

Rectal enema

Participants enrolled in the biopsy subset will also have an enema. An enema may be standard procedure prior to insertion of an anoscope or flexible sigmoidoscope since fecal matter can obscure the test. The main risk from having an enema is temporary discomfort. A hollow tube about the thickness of a pencil will be used to put approximately 120 mL of Normosol-R pH7.4 into the rectum and flush it out again (a larger volume may be required if the initial volume does not produce results), along with any stool that is there. This may cause a “bloated” or “cramping” feeling. Some air may be pumped into the rectum as well, causing flatulence. The tube is small, but it might

cause some anal or rectal discomfort if the subject has any hemorrhoids or other painful conditions.

Rectal Fluid Collection
There is the risk of mild discomfort during the collection of rectal fluid, in addition to a slight risk of bleeding with the insertion of the rectal swab and/or sponges.

Anoscopy
Insertion of a lubricated anoscope will likely cause mild discomfort

Flexible sigmoidoscopy:
Participants enrolled in the biopsy subset will have a flexible sigmoidoscopy. Flexible sigmoidoscopy is a commonly practiced endoscopic medical procedure and will not involve any increased risk over usual sigmoidoscopy performed for clinical indications. The risks associated with these procedures include mild discomfort and the feeling of having a "bloated stomach" as well as flatulence following the procedure.

Applicator
Use of a vaginal applicator to deliver a microbicide gel into the rectal compartment may be associated with minor anorectal trauma including lacerations and bruising in the anorectal area.

Directly Observed Dosing
Participants may experience embarrassment or nervousness while being observed inserting the study product or while the study product is being inserted.

Risks associated with Tenofovir 1% Gel:
The following side effects have been associated with the use of tenofovir 1% gel:

Rectal application of tenofovir 1% gel (Original or RG):

- Mild rectal fullness
- Incontinence or diarrhea
- Flatulence
- Mild abdominal pain
- Proctalgia

Vaginal application of TFV 1% gel (original):

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

13.4.2 Benefits

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

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.

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to the initiation of study procedures. Written informed consent also will be obtained for long-term specimen storage and possible future testing, although consent for 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 current DAIDS policies. Participants will be provided with copies of the informed consent forms if they are willing to receive them.

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 import to this study:

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

13.6 Participant Confidentiality

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

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent form(s), 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:

- Study monitors
- Study staff
- CONRAD
- Representatives of the US Federal Government, including NIH, the US FDA, OHRP, and/or contractors of the NIH
- Local authorities, e.g., Ministry of Health, medicine control authority
- Local IRB/EC

The MTN has applied for 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. Since the Certificate cannot be enforced outside of the US, however, it will apply only to US site staff and participants.

13.7 Special Populations

13.7.1 Pregnant Women

Women who test positive for pregnancy at the Screening or Enrollment Visit will not be eligible to participate in this study. Should a woman test positive for pregnancy after Enrollment, study product will be permanently discontinued and participants will be withdrawn from the study, per Section 7.10.2. A urine pregnancy test will be performed

on all women at scheduled study visits and additionally at interim visits as indicated; the IoR/designee will discontinue study product among participants who test positive for pregnancy. 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.

13.7.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study meets "Justifications for Exclusion" criteria for younger children as set forth by the NIH. Specifically, "insufficient data are available in adults to judge potential risk in children" and "children should not be the initial group to be involved in research studies." This study does not plan to enroll children under 21 years old.

13.8 Compensation

Pending IRB/EC approval, participants will be compensated for time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Site specific reimbursement amounts will be specified in the study informed consent form(s).

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 II. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will emphasize the unknown efficacy of the study product in preventing HIV-1 infection. In accordance with the policies of the NIH, participants must receive their HIV-1 test results to take part in this study. Condoms will be provided to heterosexually-active participants throughout the duration of their participation.

13.10.2 Care for Participants Identified as HIV-Positive

An individual who has been identified as infected with HIV-1 will be managed or referred for management according to the local standard of care. Should a woman test positive for HIV after Visit 2: Enrollment , follow-up procedures will be performed as per Section 7.10.1. Please refer to Section 9.6 for further details.

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 IRB/EC.

14 PUBLICATION POLICY

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

15 APPENDICES

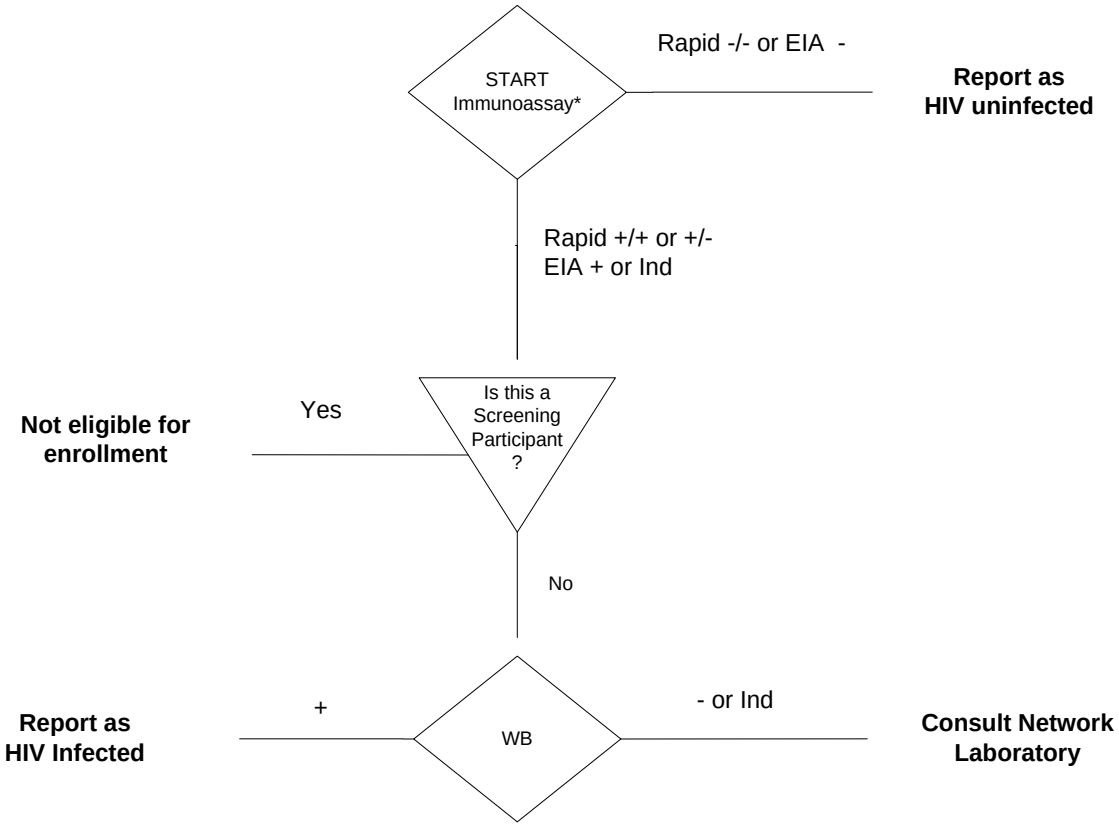
APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	Visit 1 SCR	Visit 2 ENR Study Product Admin. Visit/ Initiate Period 1 (Day 0)	Visits 3-15, Study Product Admin Visits	Visit 16 /Period 1 End. (Day 14)	Safety Phone Call	Visit 17 Washout Visit (Day 35)	Visit 18 Study Product Admin Visit/ Initiate Period 2 (Day 56-75)*	Visits 19-31 Study Product Admin Visits	Visit 32 Period 2 End/ Final Clinic (Day 70-89)*	Safety Phone Call/ Termination (Day 77-96)*
ADMINISTRATIVE AND REGULATORY										
Informed consent(s)	X									
Assignment of PTID	X									
Locator information	X	X	X	X	X	X	X	X	X	X
Demographic information	X									
Eligibility assessment	X									
Eligibility confirmation		X								
Randomization		X								
Reimbursement	X	X	X	X	~	X	X	X	X	~
Schedule next visit and/or safety phone call	*	X	*	X	*	X	X	*	X	*
BEHAVIORAL/COUNSELING										
Study Product Dosing Assessment				X					X	
HIV/STI risk reduction counseling	X	X		X		X	X		X	
Male condom counseling	X	*		*		*	*		*	
HIV pre- and post-test counseling	X	X		*		*	X		X	
Protocol adherence counseling		X		X		X	X			
Product use instructions and adherence counseling		X					X			
Biopsy procedure counseling	∞			■					■	
CLINICAL										
Medical history	X	X		X		X	X		X	
Menstrual history	X	X		X		X	X		X	
Contraceptive counseling	X	*		*		*	*		*	
Concomitant medications	X	X	X	X		X	X	X	X	
Full or targeted physical examination	X	X		X			X		X	
Pelvic examination	X	X		X			X		X	
Rectal examination	X	X		X			X		X	
Vaginal/Rectal dose observation		X	X				X	X		
Disclosure of available test results	X	X		X			X		X	
Record/update AEs			X	X	X	X	X	X	X	X
Treatment for UTI/RTI/STIs or refer	*	*	*	*		*	*	*	*	
LABORATORY (vaginal and cervical swabs as required)										
Qualitative hCG	X	X		X		X	X		X	
Dipstick UA	*	*		*			*		*	
Urine culture	*	*		*			*		*	
Urine NAAT for GC/CT		*		*			*		*	
Chemistries	X								*	
CBC with platelets	X								*	
HIV-1 serology	X	X		*		*	X		X	
PK- Blood				X			X		X	
Syphilis serology	X									
Plasma archive		X								

Vaginal NAAT for GC/CT	X									
Vaginal swabs for biomarkers		X		X			X		X	
Cervical swabs for biomarkers		X		X			X		X	
Vaginal fluid for PK				X			X		X	
CVL for PK, PD and biomarkers		◊		X			X		X	
Cervical cytobrush for PK				X					X	
Vaginal biopsies for PK and gene expression microarray	∞			■					■	
Gram stain		X		X			X		X	
Rapid Trichomonas test	X	*		*			*		*	
KOH wet mount for candidiasis	*	*		*			*		*	
Saline wet mount for BV	*	*		*			*		*	
Vaginal pH	*	X		X			X		X	
Cervical specimen for Pap smear	*									
Rectal fluid for PK, PD and biomarkers		◊		X			X		X	
Rectal biopsies for PK and gene expression microarray	∞			■					■	
STUDY PRODUCT/SUPPLIES										
Provision of study condoms	*	*	*	*		*	*	*	*	
Provision of panty liners		*	*				*	*		
Provision of study product		X	X				X	X		
Provision of lubricant		*	*				*	*		
Collect unused study product			▲	*				▲	*	

*= If indicated ∞=To be collected at the US site on all women who have not already had their screening terminated due to ineligibility (samples to be collected for gene expression only), ■= To be collected on a subset of approximately 14 US participants, ~=Sites to reference SOPs regarding participant reimbursement, ◊= PD and biomarkers only, ▲= to be performed at the final study product administration visit

APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING



*CLIA certified labs may perform 1 rapid test
Ind: Indeterminate test results
EIA: Enzyme Immunoassay

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

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

MTN-014

A PHASE 1 CROSSOVER TRIAL EVALUATING THE PHARMACOKINETICS OF TENOFOVIR REDUCED-GLYCERIN 1% GEL IN THE RECTAL AND VAGINAL COMPARTMENTS IN WOMEN

Version 2.0

May 1, 2013

PRINCIPAL INVESTIGATOR: [Sites to insert]
PHONE: [Sites to insert]
SHORT TITLE: Tenofovir Levels Following Local Application of Tenofovir Reduced-Glycerin 1% Gel

INFORMED CONSENT
You are being asked to take part in this research study because you are a healthy, HIV-uninfected, non-pregnant women between the ages of 21 to 45 years. Approximately 28 females will participate in this study at two sites. This study is funded by the United States National Institutes of Health (NIH) and CONRAD is the study sponsor. 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 consent form gives you information about the study and study staff will talk with you about it and answer any questions you may have. You may decide to stop being in the study at any time.

Do I have to join this study?
You do not have to join this study if you do not want to. It is also possible that if you want to join this study you may not be able to. It is important that you know that regardless of whether or not you join this study, your relationship with this clinic or the staff will not change. You may still get the care you need, or be referred for care. You can change your mind later if you decide to join today. You may be asked to supply the reason why you changed your mind about participating in the study. Once you read this form and are aware of the study and required procedures, you will be asked to sign your name on this form. You will be offered a copy of this form to keep.

Why is this research being done?

If you agree and are eligible to participate in this study, you will be asked to come to the clinic to use a study gel for 14 days vaginally and for 14 days rectally. The study gel contains an antiretroviral drug called tenofovir. An oral tablet form of this drug, called Viread®, is licensed, as part of a combination therapy, for the treatment of HIV, and hepatitis B in individuals 12 years of age and older. HIV is the virus that causes AIDS. Antiretroviral drugs stop or slow the activity of retroviruses such as HIV.

The main purpose of this study is to see where the study drug (tenofovir) goes, when it is applied in a gel form vaginally vs. when it is applied in a gel form rectally. We are studying the "pharmacokinetics" of tenofovir. Pharmacokinetics is the study of the way a drug enters and leaves the blood and tissue over time. For example, we will measure how much tenofovir passes from the gel and goes into the blood when used vaginally vs. rectally.

This study gel is experimental. While the gel has been tested before in men and women rectally, this is the first time the reduced-glycerin tenofovir gel will be tested vaginally. As part of the MTN-007 study 65 healthy men and women at 3 trial sites in the US inserted the gel rectally and it was found to be safe. As a follow-up to the MTN-007 study, MTN-017 will further test the safety of the reduced-glycerin tenofovir gel among 186 men and transgender women at clinical trial sites in Peru, South Africa, Thailand and the United States.

It is important that you know that a gel very similar to this one has been tested in several studies and has been found to be safe when used vaginally. For example, in CAPRISA 004 when 445 women used tenofovir gel before and after sex, it was found to be safe and effective in preventing HIV infection amongst women from KwaZulu-Natal, South Africa. Currently, former CAPRISA 004 participants are being invited to join the CAPRISA 008 Study in which they will use gel before and after sex. This study will continue to assess the safety and effectiveness of tenofovir gel when provided through family planning clinics in KwaZulu-Natal, South Africa. An additional study, the FACTS 001 study, is currently enrolling 2900 women across sites in South Africa and will provide more information on the safety and effectiveness of tenofovir gel. Results of FACTS 001 are expected mid-2015. It is important to note that the gel also appeared to be safe when used by 1007 women during the VOICE trial conducted in South Africa, Zimbabwe and Uganda, however few women used tenofovir gel as instructed (daily). The study did not show that tenofovir gel prevented women from becoming HIV infected.

The gel in this study, MTN-014, is expected to be as safe as, or safer for vaginal use than the other gel, however we cannot be sure until it has been tested in a clinical trial. If you want additional information about studies that have completed, or those that are currently ongoing, please ask a study staff member for this information and they will provide it to you.

Who will be in this research study and what will I be asked to do if I join?
Each participant will be randomly assigned (chosen "by lot" [or other equivalent local term, for example, flipping a coin]) to the order in which study product will be used. Regardless of the order assigned, all participants will use the study gel vaginally for two weeks and rectally for two weeks. Neither you nor the study staff can choose or change the order in which you will use the products.

What procedures will be performed for research purposes?

Screening Procedures –
Your first visit will happen today after you read, discuss, understand and sign this form to agree to participate. The procedures done at this visit will take about [Sites to insert time]. If all of the tests or procedures are not done today, you may come back to the clinic to complete the rest of the tests and/or procedures on another day.

Study staff will:

- Ask you where you live and how we may contact you while you are taking part in this study, ask questions about your health (including what medications you are taking), your menstrual history, and other questions to determine if you are eligible to participate in this study
- Talk with you about the requirements of this study, such as the need to abstain from inserting any non-study products into your vagina or rectum for 24 hours prior to your study visits and you must refrain from inserting any non-study vaginal or rectal products or objects into your vagina or rectum during your product use periods. These products include spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps, vaginal/rectal douches, enemas, lubricants, sex toys and tampons. Study provided lubricant may be used to assist in the rectal insertion of the study applicator. In addition, you must not take part in other research studies involving drugs, medical devices, or vaginal/rectal products for the whole time you are in this study.
- Perform a physical exam and other procedures and tests to better understand your health
- Perform a rectal exam. The study doctor or nurse will look at the outside of your anus and the area around your anus. He/she will then insert a lubricated gloved finger, into the anal canal to check for any issues.
- Perform a pelvic examination:
    - The study doctor or nurse will use a speculum, a plastic or metal instrument used to separate the walls of the vagina. The study doctor or nurse will check your vagina and cervix for signs of infection, and other problems. They will also take some fluids to test for sexually transmitted infections or diseases (commonly known as STIs or STDs) and other possible problems (e.g., reproductive tract infections (RTIs)), if they feel it is necessary.

    - The study staff may also collect samples from your cervix for a Pap smear if you do not have results with you today of a Pap smear that was done in the past 12 months (a Pap smear is a test for cervical cancer). It takes about [Sites to insert amount of time] before Pap test results are ready. If your Pap result is not normal, you might not be able to be in the study; the study staff can discuss this with you.
- Talk with you about HIV, HIV testing, and ways to prevent HIV and other infections passed through sex
- Take a blood sample [site to insert amount] to test for:
    - Health of your blood, liver and kidneys
    - Infections passed through sex, including HIV
        - You will be told your HIV test result as soon as it is available [*sites to add expected timeframe*]. You will talk with the study staff about the meaning of your tests and feelings you may have about the results. 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 HIV test results to be in the study. If the test shows that 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 if there are other studies you may be eligible for.
- Ask you to provide a urine sample to test for pregnancy. If you are pregnant, you will not be able to participate in this study. The study staff will tell you where you can find care for your pregnancy. This study does not provide pregnancy care. You will talk with study staff about contraception and ways to avoid getting pregnant
- Give you male condoms if you are sexually-active with a male, or, if you need them
- Give you treatment, or tell you where you can find treatment, for infections other than HIV passed through sex and urinary tract infections, if you need treatment. This study does not provide care or treatment for HIV.
- Give you information for other services, if needed
- Results of tests listed above will be available within [site to specify timeframe] of your visit. The study staff will review your test results with you when they are available.

Tissue Samples

Approximately 14 participants from the United States [*Site participating in the Rectal and Vaginal Tissue Subset to insert the following language:*, all of the participants at this site,] will provide rectal and vaginal tissue (biopsies) to help researchers better understand the how the study drug enters and exits the body and what effect the drug has on the tissue, including what effect the study drug has on your genes.

[Site not participating in the Rectal and Vaginal Tissue Subset please insert the following language:]

This research site is not participating in the collection of these extra samples.

[Sites participating in the Rectal and Vaginal Tissue Subset please insert the following language:]

If you agree to take part in this study, you will have an exam of your vagina using a speculum and an exam of your rectum using flexible sigmoidoscopy. A flexible sigmoidoscopy is when a flexible, hollow tube is placed inside your rectum so that the study doctor can take a sample of rectal tissue. In preparation for the rectal tissue sample collection you will have an enema. For the enema, a hollow tube about the thickness of a pencil will be used to put some fluid into your rectum to flush it out. This may need to be repeated so that any stool that is there is removed.

Study clinicians will take approximately 1 small tissue sample from the vagina and 1 small tissue sample from your rectum at your visit today, each about the size of a grain of rice. These samples will be used to look at the activity of some of your genes today and compare them to the tissue collected after you use study product. However, if you are found to be ineligible for this study, these samples will be destroyed.

At Screening, Visit 16 and Visit 32 more biopsies will be collected, see below:

Visit	**Number of biopsies collected**	
	Vaginal	**Rectal**
Screening	1	1
Visit 16: Period 1 End Visit (Day 14)	3	6
Visit 32: Period 2 End Visit (Day 70-89)	3	6
Total	7	13

Study staff will talk to you about a few of important things to avoid doing prior to and following the collection of your biopsies. It is important that you do not put any non-study product in your rectum or vagina for 3 days before the collection of the biopsies or for 3 days after, this includes having vaginal sex and anal sex, because you may be at higher risk for getting or spreading an infection until the biopsy sites have healed. It is important that you continue to use condoms every time you have sex, regardless of how many days it has been since your biopsies were collected. If you have inserted anything into your rectum or vagina in the past 3 days it is important that you tell a member of the study staff. You should also not take medicine that may cause you to bleed easily for 3 days prior to the collection of these samples and for 3 days after the collection of the samples. Study staff can tell you which medicines to avoid.

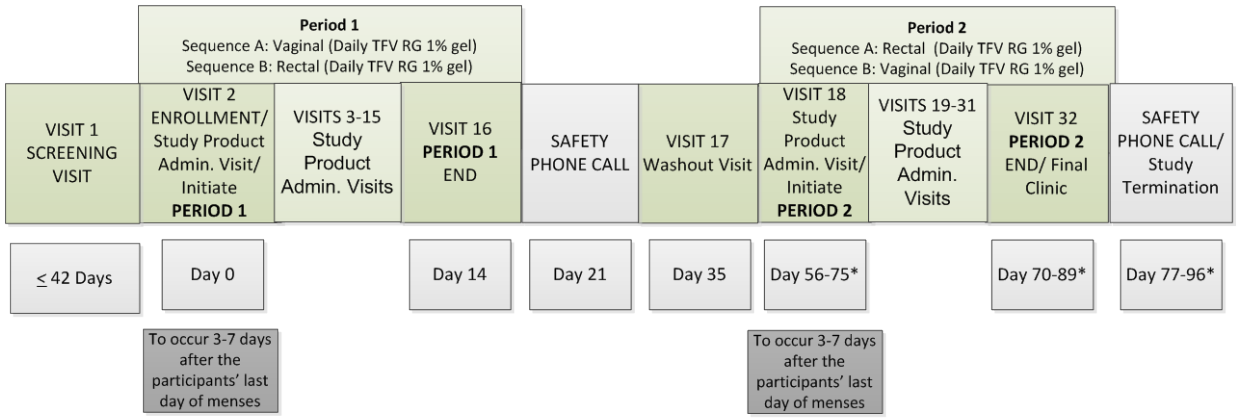
Enrollment and Follow-up Procedures –
If you are eligible, your next visit will be within 42 days of today's visit. That visit is called, Enrollment/Study Product Admin./Initiate Period 1 Visit (Visit 2).

This study has 2 periods and each period lasts about two weeks. You will begin using study product at the Enrollment/Study Product Admin./Initiate Period 1 Visit (Visit 2). Your Period Start Visits will need to fall approximately 3-7 days after the last day of your period. You will use the study product rectally for 14 days and vaginally for 14 days. During the two periods you will be asked to come into the clinic every day, including Saturdays and Sundays to insert the study gel in the clinic. The insertion of this gel will be observed. This means that study staff will watch you insert the gel [Site to insert as appropriate: or will assist you with inserting the gel, if needed].The periods are separated by an approximately 6 week washout period. A washout period can be described as a period of time when participants do not take study product. This period of time will ensure that the study drug has time to leave your body before you begin using study product in Period 2. You will come into the clinic once during this washout period.

You will be in the study for approximately 10-13 weeks, depending upon the timing of your menstrual cycle, from the time you enter the study up until your follow-up phone call at the end of the study. The study visit schedule may change and be longer depending upon your menstrual cycle, because it is important that you start using the product around the same time in your cycle for both periods. You will use the study gel for a total of 28 days. You will never use the study product more than 14 days in a row, and it is important that you come into the clinic for each dose. You will be given extra doses during each period in the event that you are not able to make it to the clinic [Site to insert as appropriate: or able to make alternative arrangements with study staff to bring you study gel and observe the administration of the product]. When gel is administered at home, it should be applied at approximately the same time of day as all other doses, if possible.

The visits when you come to the clinic to insert your gel will take [insert approximate of time]. The other visits will take [insert approximate of time].

The visit schedule is shown below:



* Visit schedule will vary depending upon your period.

At your Enrollment Visit, you will have the following study procedures:

- At your Enrollment Visit/ Period 1 Start, you will answer questions to confirm that you are able to join the study including whether you are using an effective method of contraception and intending to use that method for the entire time that you are in this study. Acceptable methods of contraception for this study include:
    - Hormonal methods, except vaginal rings
    - Intrauterine device (IUD) inserted at least 42 days prior to Enrollment
    - Sterilization of participant or partner at least 42 days prior to Enrollment
    - Self-identifies as a woman who has sex with women exclusively
    - Sexually abstinent for the past 90 days and the intention to remain sexually abstinent for the duration of study participation

- You must agree to refrain from inserting any non-study vaginal or rectal products or objects into the vagina or rectum during your study product use periods. In addition, 24 hours before the Enrollment Visit, Study Product Administration/Initiate Period 2 Visit, and Period End Visits you must agree to abstain from inserting any non-study product or object into your vagina or rectum.
- Also at the Enrollment Visit, if you are found to be eligible, you will be told the order in which you will use the study product.
- Study product will be inserted in the clinic. You will be asked to come into the clinic [or meet with study staff at an alternative location] every day for the next 13 days to use study gel, this same visit schedule will be repeated during the second period.
- Provide a blood sample [insert amount] in case there is a question about your lab results in the future. After all testing is done, this sample will be destroyed according to the site's procedure for getting rid of blood samples that will not be needed after the study ends.

Throughout the study, you will be asked to:

- Provide updated information about where you live and how to contact you
- Tell study staff if you have experienced any changes in your health, menstrual history, including changes to your medicine, or any problems related to the study since your last visit
- Schedule your next visit or study contact

You will also receive counseling. You will talk with study staff about:

- When and how to use the study gel
- How to follow the rules of the study
- Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to prevent HIV and other infections passed through sex

The following clinical procedures will be performed at some visits (but not the visits when you only come into the clinic to insert the gel):

- A physical exam
- A blood sample [sites to insert amount] will be taken to test:
    - How much of the study product is in your body
    - For infections passed through sex, including HIV
        - You must receive your HIV test results to stay in the study. You will talk with study staff about the meaning of your tests and about feelings you may have about the results. If your HIV test is positive, you may be offered additional blood tests, [sites to insert blood volumes per local regulatory requirements- XX mL] if the study doctor and researchers think that it would benefit you. Study staff will provide you more information about additional blood tests if the tests are determined to be needed. You will be referred to available sources of medical care and other services that you may need.
- A urine sample will be collected to test for pregnancy
- A rectal exam will be performed at period initiation and period end visits. To collect these samples the clinician and/or designee will need to insert a short hollow tube called an anoscope inside your rectum. The clinician will insert swabs and/or sponges through the hollow tube to test:
        - How your rectal fluids protect against HIV in the laboratory
        - How much of the study product is in your rectal fluids
- A pelvic exam will be performed at period initiation and period end visits. Vaginal and/or cervical fluid will be taken and may be used to test:
    - For infections passed through sex
    - How your vaginal fluids protect against HIV in the laboratory
    - How much of the study drug is in your vaginal fluids
    - A laboratory in the United States will also test vaginal and cervical fluid to look for proteins and cytokines. Cytokines are very small parts of the

fluid that sometimes can be seen when there is inflammation. The protective proteins may help to protect women from infections. These tests do not say if a person has a certain disease or infection. In the future, these tests may help scientists learn more about the safety of different vaginal products. They will also look at how the drug affects the cells in your body. Because doctors do not yet understand enough about what these test results might mean, the results will only be seen by the researchers.

- A cervicovaginal lavage (CVL) will be performed at period initiation and period end visits. For CVL, a clinician rinses your vagina and cervix with about 2 teaspoons [SITES TO INSERT LOCAL EQUIVALENT] of sterile fluid and collects that fluid into a tube for testing. This fluid will be used to look for proteins and cytokines. Researchers will also use this fluid to see how it protects against HIV in the laboratory and how much of the study drug is in your vaginal fluids

As part of the clinical procedures you will:

- Receive treatment or be referred for treatment for problems (including infections passed through sex) that the study staff may find. You may also be offered male condoms if you heterosexually-active
- Receive test results, when they are available
- Talk with a clinician about ways to avoid pregnancy, if needed.

You will be asked to use study product for 2 weeks vaginally and for 2 weeks rectally; as part of using study product you will:

- Receive study gel to be used daily and talk with study staff about how to correctly use the gel.
- Be asked to come into the clinic to insert your study gel. [*Site allowing off-site visits:* Alternatively, you can make arrangements with study staff to meet you at a location that is convenient for you and the study staff.]
- You will receive lubricant to aid in inserting the gel applicator rectally, if needed
- You will receive panty liners to use if you need them.
- Be asked to bring unused gel applicators with you to your period end visits
- Be called by study staff about one week after Period 1 end visit and one week after Period 2 end visit, so that you can report any health problems or other problems since your last visit. You can always call study staff if you have any problems related to the study product or your participation in this study.

Other Procedures:

- If you are having health problems or there is a change in your health, the doctor may perform other tests or ask you to return to the clinic more often
- You will get treatment or be referred for treatment for most types of sexually transmitted infections, if you need it

What are the possible risks, side effects, and discomforts of this research study?

Risks from tenofovir gel:
The gel can cause side effects. Vaginal use of tenofovir gel has resulted in vaginal candidiasis, discharge from the vagina, irritation in the genital area, and diarrhea. We do not yet know all the side effects of tenofovir gel on the rectum. Men and women who have used the gel rectally have experienced incontinence, a feeling of mild rectal fullness or bloating, gas, mild abdominal pain, or crampy pain in the rectum when using the gel rectally.

Risks from phlebotomy (blood tests)
- You may feel discomfort or pain when your blood is drawn
- You may feel dizzy or faint
- You may have a bruise, swelling, small clot, or infection where the needle goes in your arm or finger

Risks of finger and anoscope rectal exams
- You may feel discomfort or pressure when your rectum is examined
- You may experience some discomfort when fluid is collected, and occasionally minor rectal bleeding may occur

Risks of genital exams:
- During or after genital exams, you may experience embarrassment. You may have discomfort or feel pressure in your genital area and inside your vagina or have slight vaginal bleeding which will stop shortly after the examination.

Risks from the applicator:
- You may experience some discomfort from the applicator since the applicator has been designed for a vaginal rather than rectal use. Inserting the applicator may result in lacerations and/or bruising.

Other possible risks:
- You may become embarrassed, worried, or nervous answering personal questions about your sexual behavior, discussing ways to protect against HIV and other infections passed during sex, and your test results
- You may become embarrassed or nervous while study product use is being observed
- We will make every effort to protect your privacy while you are having the study visits, exams, and tests. Reports via paper or computer will be stored in computers that are password-protected and will not include personal information

that could identify or link information to you; only your study ID number will be recorded.

- You may become worried or nervous while waiting for your test results
- If you have HIV or other infections, knowing this could make you worried or nervous. Finding out this information may also cause you problems with your partner, if you have one. A trained counselor 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. Also, you could face problems in your relationships associated with study product use. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.
- If you become infected with HIV while using gel, it is possible that Tenofovir and Truvada (which contains medications that inhibit HIV, tenofovir and emtricitabine) would not work against the HIV in your body, when you do need treatment for HIV infection. 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 may also do blood tests that will show which HIV medications might work best for you. If you become HIV positive during this study and are referred to other studies blood tests can be done that will show which HIV medications might work best for you

[Sites participating in the Vaginal/Rectal Tissue Subset please insert the following language:]

Vaginal and Rectal Tissue Samples:

- During the enema you may experience temporary discomfort and flatulence or gas
- You may experience some mild discomfort, flatulence or gas, and feel like you have a “bloated stomach” from the air from the flexible sigmoidoscope
- Even though the risk is low, you may experience infection, mild rectal irritation and may feel a sudden urge to have a bowel movement
- You may experience limited bleeding (1 to 2 days after the procedure) related to the biopsies. It is important that you inform physicians if you have a history of bleeding. If you have bleeding heavier than your usual menstrual period, a foul odor or a heavier vaginal discharge (more than usual), you should contact the study clinic right away. There is a small risk of the biopsy area becoming infected or having bleeding that is heavier than spotting.
- You may experience low blood pressure
- Even though the risk is very rare, there is a chance that you may have a hole or a tear in the intestine. This happens once out of every 1,000 procedures. If this were to happen, surgery to repair the tear may be necessary.

What are possible benefits from taking part in this study?
There are no direct benefits for taking part in this study, but you or others may have future benefit from information learned in this study. You may also learn more about HIV and other diseases and ways to protect yourself from infection. It is important that you know, however, that you will not be paid any additional money (beyond the reimbursement described below for study participation) if the study product being studied is eventually licensed for use.

You will have physical and rectal exams. If these tests show that you might have any health problems, you will be told about medical care and other services available to you. This will be available to you even if you do not enroll in this study.

You will get counseling and free condoms. If you have infections passed through sex, other than HIV infection, you will be offered medicine to treat them or provided information for where you may receive treatment. This treatment or referral for treatment is available to you even if you do not enroll in this study.

This study does not provide medication for treatment of HIV/AIDS. If you become infected with HIV, you will be told where you can go for medical care, counseling, and other services.

What if there is new information learned during this study?
We will tell you about new information from this or other studies that may affect your willingness to stay in this study.

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

- The study is cancelled by the US Food and Drug Administration (FDA), US NIH, CONRAD (the company that supplies the gel), the US Office for Human Research Protections (OHRP), the MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/ the Ethics Committee (EC). An IRB is a committee that watches over the safety and rights of research participants
- The Study Monitoring Committee (SMC) recommends that the study be stopped early (A SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study)
- You are found to be infected with HIV
- You become pregnant. The effects of the study gel on a developing human fetus are unknown. If you become pregnant during the study, study staff will refer you to available medical care and other services you or your baby may need. The study does not pay for your care if you become pregnant. *[Sites to*

include/amend the following: We may also contact you about a study that collects information about pregnancy and babies up to one year old.] The outcome of your pregnancy is important to study staff; therefore, your pregnancy will be followed until the results of your pregnancy are known.
- You begin breastfeeding
- You require a treatment that may not be taken while using the study product, but depending on your treatment you may continue in the study, it is important that you let study staff know exactly what medicines you are taking.
- You are unable or unwilling to follow study instructions
- You cannot come to appointments
- Other administrative reasons

The study doctor may ask you to stop using the study product but continue to come in for follow-up visits and procedures if:

- You are unwilling to comply with study procedures
- A study doctor decides that using the gel would be harmful to your health
- You require a treatment that may not be taken while using the study product

If you stop using the study product, but continue to come in for follow-up visits, your visit schedule and procedures may be modified. Study staff will provide you with more information as changes in your schedule and procedures, as needed.

Will there be any payments if I take part in this research study?
[*Site to insert information about local reimbursement:*] You will receive [*Site to insert amount* xx] for your time, effort, and travel to and from the clinic at each scheduled visit. You will receive [Site to insert amount xx] for any visits which occur in between your normally scheduled visits, these are called interim visits. For phone calls you will receive [Site to insert amount xx]. You will not receive payment for costs associated with your pregnancy, if you become pregnant, or for your HIV-related care, if you become infected with HIV.

[US Sites to insert the following US Internal Revenue Service reporting, as applicable: This compensation for your time, effort and travel is taxable income. If the amount paid to you exceeds $600 within a calendar year, [your site] will file an IRS form 1099 with the Internal Revenue Service and will mail you a copy.]

What are the costs?
There is no cost to you for study-related visits, study product, physical exam, laboratory tests or other procedures. [*Site to include additional information as applicable according to site capacity.]*

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

Who will know about my participation in this research study?
Any information about you obtained from this research will be kept as private as possible. All records related to your involvement in this research study will be kept in a [site to insert]. Your identity on these records will be indicated by a number rather than by your name, and the information linking these numbers with your name will be kept separate from the research records.

Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally. *[Sites to insert if applicable:]* The study staff may use your personal information to verify that you are not in any other research studies.

Your records may be reviewed by:
- Study monitors
- Study staff
- CONRAD, the organization that supplies the study gel
- Representatives of the US Federal Government, including NIH, the US FDA, OHRP, and/or contractors of the NIH
- [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [Insert names of applicable IRBs/ECs]

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

[*US site to include*:]
In addition to the efforts made by staff to keep your personal information confidential, a Certificate of Confidentiality has been applied for from the US Federal Government for this study. 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 provide for study purposes. However, if the study

staff learns of possible child, elder or dependent adult 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 or your participation in the study.

What if I am injured as a result of participating in this study?
[Sites to specify institutional policy:] 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. This institution or the United States National Institutes of Health does not have a program to provide money for injuries. You will be told where you can receive additional treatment for injuries, if needed.

May I withdraw my consent for participation in this research study?
[Sites to specify institutional policy:] Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. If you choose to stop participation or to leave the study, you will not lose the benefits of this clinic, nor will the confidentiality of the care provided for you here be affected. You should feel free to come back to this facility even if you decide not to participate in this study. If you want the overall results of the study after the study is over, let the study staff members know.

What other choices do I have besides this study?
You do not have to participate in this study, if you choose not to do so. Please talk to your doctor about these and other choices that may be available to you.

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

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

If you have questions about whom to contact at the research site, you should contact [INSERT NAME OF THE INVESTIGATOR OR COMMUNITY EDUCATOR OR CAB MEMBER [STAFF WILL DECIDE WHICH]] at [INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER].

Can my private health information and samples collected by this study be used for future studies?

There might be a small amount of your biological specimens, such as urine, blood, vaginal, cervical and rectal samples, left over after we have done all of the study-related testing after your study visits. We would like to ask your permission to store these samples and health data related to these samples for use in future studies. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range. If you agree, your samples and related health data will be stored safely and securely at facilities that are designed so that only approved researchers will have access to the samples. [*Non-US site(s) to insert*: Some of these research facilities may be outside of your country.] Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. You can still enroll in this study if you decide not to have these samples stored for future studies. If you do not want the samples stored, we will destroy the leftover specimens. Any future studies that may be done will also have to be approved by an IRB/EC. [*Sites to specify institutional policy:*] There is no time limit on how long your samples or health data will be stored or when these leftover specimens may be tested.

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

_____ Initials & Date — I do not agree to allow my biological specimens and health data to be used in future research studies.

[*Sites to include/amend the following, if applicable:*]

CONSENT FOR OFF-SITE VISITS

Members of the research team at this clinic may be able to visit you at a location other than the study clinic as part of the study. Some of the scheduled study visits (Study Product Administration Visits) may take place at a location other than the study clinic, if you agree. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the duration) and procedures to ensure confidentiality. However it is important that you know that off site visits may affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

To conduct visits outside of the clinic we will need your consent. Please read carefully the following statement and initial and date one option. You can choose to not to be visited outside of the study clinic and still participate in this study. You can withdraw your consent for off site visits at any time by providing your request

in writing to the person in charge of this study.

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

Initials and Date

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

Initials and Date

SIGNATURES- VOLUNTARY CONSENT

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

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

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