MTN-019

Phase 2 Expanded Safety Study of Tenofovir Gel in Pregnancy

Microbicide Trials Network

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases

Funded by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
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26 October 2011

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine transaminase
ANRS	Agence Nationale recherché sur le sida et les hépatites virales
AOR	adjusted odds ratio
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
BMD	bone mineral density
BV	bacterial vaginosis
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CORE	Coordinating and Operations Center
CRF	case report form
CRPMC	Clinical Research Products Management Center
CWG	Community Working Group
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EAE	Expedited Adverse Event
EC	Ethics Committee
FDA	Food and Drug Administration
FHCRC	Fred Hutchison Cancer Research Center
fmol	femtomole
FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practices
GEE	generalized estimating equation
gm	gram
HBsAg	hepatitis B surface antigen
HC	head circumference
HEC	hydroxyethylcellulose
HELLP	hemolysis, elevated liver enzymes, low platelet count
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
IATA	International Air Transport Association
IC_{50}	50% inhibitory concentration
ICF	informed consent form
IGF	insulin-like growth factor
IND	Investigational New Drug
IoR	Investigator of Record
IRB	Institutional Review Board
IRR	incidence rate ratio
LBW	low birth weight
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantitation

MAA	multi-assay algorithm
mg	milligram
MTN	Microbicide Trials Network
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
NIAID	National Institute of Allergy and Infectious Disease
NICHD	National Institute of Child Health and Human Development
NIMH	National Institute of Mental Health
NIH	(United States) National Institutes of Health
NL	Network Laboratory
NVP	nevirapine
OB	obstetric
OHRP	Office for Human Research Protections
p-y	person-years
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PEPI	Post Exposure Prophylaxis of Infants Study
PHACS	Pediatric HIV/AIDS Cohort Study
PK	pharmacokinetic(s)
PMPA	9-R-2-phosphonomethoxypropyl adenine
PPD	Pharmaceutical Product Development
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PROMISE	Promoting Maternal-Infant Survival Everywhere
PSRT	Protocol Safety Review Team
PSS	polystyrene sulfonate
PTID	participant identification number
qd	quaque die (daily)
RE	regulatory entity
RNA	ribonucleic acid
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	Statistical Data Management Center
sdNVP	single-dose nevirapine
SMARTT	Surveillance Monitoring of Antiretroviral Toxicity
SMC	Study Monitoring Committee
SOP	standard operating procedure(s)
SSP	study specific procedures
STI	sexually transmitted infection
SUSAR	suspected unexpected serious adverse reaction
TDF	tenofovir disoproxil fumarate
TEmAA	Tenofovir/Emtricitabine in Africa and Asia (Study)
TERIS	Teratogen Information System
TFV	tenofovir
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VS	vital signs
w-y	woman-years
WB	Western blot
ZDV	zidovudine

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MTN-019

Phase 2 Expanded Safety Study of Tenofovir Gel in Pregnancy

INVESTIGATOR SIGNATURE FORM

Version 1.0

26 October 2011

A Study of the Microbicide Trials Network

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases

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

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 product 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, NICHD, NIMH, and CONRAD for review prior to submission.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the product 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-019

Phase 2 Expanded Safety Study of Tenofovir Gel in Pregnancy

PROTOCOL SUMMARY

Short Title: Phase 2 Study of Tenofovir Gel in Pregnancy

IND Sponsor: Division of AIDS, NIAID, US NIH

Protocol Chairs: Richard H. Beigi, MD, MSc
Bonus Makanani, MBBS, FCOG (SA)

Sample Size: Approximately 384 women and their newborns

Study Population: Healthy, sexually active, HIV-uninfected pregnant women, 18 – 45 years old, with a singleton pregnancy, without evidence of maternal or fetal complications in the current pregnancy, and their newborn infants

Study Sites: Study sites selected by the MTN Executive Committee

Study Design: Double-blinded, multi-site, two-arm, randomized, placebo-controlled trial of daily vaginal use of 1% tenofovir gel vs. Universal Placebo gel with onset of 28-day dosing period to occur within the following gestational age ranges:

Group 1:	36 0/7 weeks – 37 6/7 weeks	(114 women)
Group 2:	28 0/7 weeks – 32 6/7 weeks	(90 women)
Group 3:	20 0/7 weeks – 24 6/7 weeks	(90 women)
Group 4:	12 0/7 weeks – 16 6/7 weeks	(90 women)

Groups will be filled sequentially. Group 1 is larger than the other groups, based on rate of anticipated delivery prior to scheduled end of dosing (see Section 10.4).

At any point during the study, the Protocol Safety Review Team, DAIDS Medical Officer, or MTN Study Monitoring Committee may pause enrollment and/or study product dosing for further review of safety data.

Study Duration: Approximately 30 months for total study duration

Study Products: 1% tenofovir gel
Universal Placebo gel

Study Regimen: One applicator of study gel per vagina daily for 28 days or until pregnancy outcome, whichever comes first

Primary Objective:

- To describe the safety profile of 1% tenofovir gel used daily per vagina for up to 28 days during different gestational age ranges during pregnancy

Primary Endpoints:

- Maternal outcomes
    - Grade 2 or higher adverse events (AEs) in the following categories
        - Specific laboratory abnormalities
            - Alanine transaminase (ALT)
            - Aspartate aminotransferase (AST)
            - Creatinine
        - Specific genital/pelvic signs/symptoms
            - Dyspareunia
            - Pain (vulvar, vaginal, and/or pelvic)
            - Tenderness (vulvar, vaginal, and/or pelvic)
            - Itching (vulvar and/or vaginal)
            - Edema (vulvar, vaginal, and/or cervical)
            - Erythema (vulvar, vaginal, and/or cervical)
            - Lesions (vulvar, vaginal, and/or cervical)
            - Vulvar rash
            - Vaginal dryness
            - Dysuria
            - Vulvovaginitis
            - Cervicitis
        - Pregnancy complications
            - Genital bleeding
            - Preterm labor
            - Spontaneous preterm delivery
            - Chorioamnionitis
            - Postpartum endometritis
            - Gestational hypertension and/or pre-eclampsia
            - Gestational diabetes
            - Sepsis
            - Abruptio placentae
            - Postpartum hemorrhage
            - Premature rupture of membranes (prior to onset of labor, at term or preterm)

- For AEs not included above, Grade 3 or higher events judged by the investigator to be related to the study gel or applicator
    - All serious adverse events
- Pregnancy outcomes
- Neonatal outcomes (first 30 days of life)
    - All serious adverse events

Secondary Objectives:

- **Pharmacokinetics.** To establish the peak blood concentration and the time course over the first 6 hours after a vaginal dose of tenofovir under steady-state vaginal dosing conditions during pregnancy
- **Adherence.** To assess the adherence to daily use per vagina of 1% tenofovir gel for 28 days among pregnant women

Secondary Endpoints

- **Pharmacokinetics**
    - Maternal blood levels of tenofovir
- **Adherence**
    - Self-reported product use captured through questionnaires
    - Study drug levels
    - Count of returned unused applicators

Exploratory Objectives:

- **Vaginal Microenvironment.** To describe vaginal microenvironment changes associated with tenofovir 1% gel used daily during different gestational age ranges during pregnancy
- **Behavior.** To describe sexual activity, condom use and intravaginal practices during different gestational age ranges of pregnancy
- **Acceptability.** To explore participant acceptability of study product use in pregnancy
- **Pharmacokinetic.** To describe maternal:cord blood ratios for those participants who deliver during study product dosing

- **Adherence.** To compare participant self-report vs. electronic monitoring of study product adherence to a daily regimen of vaginally applied 1% tenofovir gel over 28 days of use (at sites with capacity)

Exploratory Endpoints:

- **Vaginal Microenvironment**
  - Gram stained vaginal smears
  - Vaginal pH
  - Identification of vaginal microorganisms at sites approved by NL
  - Genital biomarker expression (selected by the MTN Biomedical Science Working Group) in vaginal and cervical secretions

- **Behavior**
  - Self-report via questionnaire

- **Acceptability**
  - Self-report via questionnaire

- **Pharmacokinetics**
  - Cord blood levels of tenofovir for infants of mothers who dosed within 24 hours of arriving at the hospital for delivery

- **Adherence**
  - Number of days in which the study product was used as reported electronically (at sites with capacity)

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: Phase 2 Expanded Safety Study of Tenofovir Gel in Pregnancy

Protocol Number: MTN-019

Short Title: Phase 2 Study of Tenofovir Gel in Pregnancy

Date: 26 October 2011

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2 INTRODUCTION

2.1 Rationale for Studying 1% Tenofovir Gel in Pregnancy

Potential Licensure of 1% Tenofovir Gel

After more than 15 years of research on the antiretroviral (ARV) drug tenofovir as a potential agent for human immunodeficiency virus (HIV) prevention, the results of CAPRISA 004 showed a 39% reduction in the risk of HIV infection for women randomized to a coitally dependent regimen of 1% tenofovir (TFV) gel and approximately 50% reduction in the risk of acquiring herpes simplex virus Type 2 (HSV-2).[1] Since these results were announced, significant attention has been given to the possible licensure of tenofovir gel as an agent for HIV prevention in women, as well as key remaining research questions to be answered before potential roll-out of the gel in the public sector. In November 2010, representatives from US NIH and the MTN convened a meeting of African and US experts from diverse fields, including obstetrics and gynecology, pharmacology, infectious disease, ethics, and others, to discuss next steps for the evaluation of antiretroviral drugs for HIV prevention in pregnancy and lactation. Meeting attendees identified several key research gaps requiring further investigation, as well as possible studies to address these gaps. Evaluation of the safety of topical TFV in the second and early third trimesters of pregnancy was identified as one of these critical areas. With input from meeting attendees, including African and US site investigators, the MTN-019 protocol was designed to provide crucial information on the extended safety in pregnancy of daily use of TFV gel, a product already with substantial data to suggest a safe profile in pregnancy. Obtaining these data in a carefully monitored clinical trial prior to potential TFV gel licensure and public access will inform safe product use by reproductive age women and accurate drug labeling by regulators, a key advantage noted by the US Food and Drug Administration (FDA).[2] The Institute of Medicine, when commenting on the methodological challenges of HIV prevention trials, included among its key recommendations the need to evaluate the potential effects candidate HIV prevention agents may have on pregnant women and their fetuses.[3]

The VOICE Study – Vaginal and Oral Interventions to Control the Epidemic – is a trial evaluating two different approaches for preventing the sexual transmission of HIV in

women.[4] VOICE was designed to test daily use of oral tenofovir disoproxil fumarate (TDF) (Viread®) and emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) (Truvada®), drugs that are routinely used as part of combination therapy for treating HIV; and daily use of the ARV-based candidate microbicide, 1% TFV gel. The study, which began September 2009, completed enrollment of 5,029 sexually active HIV-negative women at sites in Zimbabwe, Uganda and South Africa in June 2011. In September 2011, the oral TDF tablet arm was stopped due to a finding of futility at interim data review. Final study results are expected in early 2013. The US FDA has commented on the possibility that VOICE may be considered a confirmatory trial for CAPRISA 004, depending on results, and that additional data on safety of tenofovir gel in pregnancy is important pending data.[5]

Primary HIV Infection in Pregnancy and Higher Risk of *in utero* Transmission

Recent findings from Post Exposure Prophylaxis of Infants (PEPI)-Malawi and other trials demonstrate the association between recent HIV infection and the likelihood of *in utero* HIV transmission.[6] The PEPI-Malawi trial used a multi-assay algorithm (MAA) to identify recent HIV infection and to evaluate the association between recent maternal HIV infection and *in utero* transmission of HIV. Plasma samples were collected at delivery from 2,561 HIV-infected women and logistic regression models assessed association between recent HIV infection and *in utero* HIV transmission (defined as a positive infant HIV deoxyribonucleic acid (DNA) test at birth). Seventy-three women were identified as recently infected using the MAA. Those women were younger and had lower parity than women who were identified as not recently infected using the MAA ($P < 0.0001$ for age and parity). The frequency of *in utero* HIV transmission was 17.8% among women identified as recently infected, compared to 6.7% among women identified as not recently infected (13/73 vs. 166/2488, $P = 0.001$). In a multivariate model, three factors were independently associated with *in utero* HIV transmission: recent infection (adjusted odds ratio [AOR]: 2.49, 95% CI: 1.30-4.78, $P = 0.006$), $\log_{10}$ HIV viral load at delivery (AOR: 2.01, 95% CI: 1.60-2.51, $P < 0.0001$), and younger age (per 10-year increase, AOR: 0.66, 95% CI: 0.43-0.93, $P = 0.02$).

Results obtained using the MAA suggest that recent maternal HIV acquisition is strongly associated with *in utero* HIV transmission, independent of HIV viral load at delivery. These findings reinforce the case made by previous analyses pointing to pregnancy as a high-risk time for incident HIV infection[7-8] and high risk of maternal to child transmission due to high viral loads at time of delivery. Risk of transmission to infant with primary maternal HIV infection in pregnancy was noted to be 15-fold higher in one US study.[9] In Botswana, the transmission rate to infant was noted to be 73% among women who seroconverted during pregnancy or lactation, compared to 4.7% among women entering pregnancy already HIV seropositive; seroconversion in pregnancy accounted for 43% of infant HIV infections in Botswana in 2007.[8]

Seroconversion Rates in Pregnancy

Acquisition of HIV during pregnancy is common and has been estimated at rates that equal or exceed rates in non-pregnant women.[7, 10-13] For populations of pregnant women in sub-Saharan Africa, HIV acquisition has been estimated at significant rates:

- Uganda 2.3 per 100 woman-years (w-y) of pregnancy[7]
- Uganda 4.0 per 100 w-y of pregnancy[10]
- Botswana 1.3 per 100 w-y of pregnancy[8]
- Zimbabwe 1.6 per 100 w-y of pregnancy[14]
- South Africa 5.2 per 100 w-y of pregnancy[15]
- South Africa 10.7 per 100 w-y of pregnancy[13]

Pregnancy as a period for risk of HIV infection is not limited to sub-Saharan Africa. In the United States, six (11%) of 54 women with positive HIV rapid tests at delivery had primary HIV infection during pregnancy.[16] Thus, substantial evidence supports the special importance of pregnancy as a time for primary HIV prevention.

Primary Herpes Simplex Virus Infection in Pregnancy

If TFV gel is confirmed to be safe and effective for prevention of HIV in non-pregnant women via the VOICE trial, it may have great potential to impact the HIV/AIDS (acquired immunodeficiency syndrome) epidemic, including the epidemic among pregnant women and their infants. However, the aforementioned risk reduction for HSV-2 acquisition also has special significance for the use of this product by pregnant women. Infection with HSV in pregnancy carries with it a significant health risk for the newborn. Neonatal HSV can lead to disseminated or central nervous system (CNS) disease in 50% of cases. Despite early high dose antiviral therapy, disseminated HSV infection carries a case fatality rate of 50%; 40% of survivors of CNS disease will have neurologic sequelae.[17] The vast majority of cases are acquired when the neonate is exposed to maternal secretions as it passes through the birth canal, and the stage of maternal infection at the time of delivery is an important risk factor for neonatal transmission. In a large US cohort study of over 40,000 women, a first episode of HSV carried a relative risk of neonatal transmission of 59.3 (6.7-525) compared to recurrent disease, when adjusted for type of delivery, maternal age, and premature delivery.[18] Acquisition of HSV during pregnancy is also associated with high titers of virus in genital secretions for up to three months after initial infection.[19] Of note, recent *in vitro* work demonstrated that the concentration achieved intravaginally with a 1% tenofovir topical gel has direct antiherpetic activity.[20]

Pregnancy Common within and Outside of Clinical Trials

At this time, the pregnancy incidence rate in VOICE is approximately 6.6 per 100 w-y (MTN SDMC, personal communication). While this rate is still lower than the 11% observed over the course of HIV Prevention Trials Network (HPTN) 035, another Phase 2B microbicide trial, VOICE has completed only about 42% of anticipated w-y of follow-up. Substantial rates of pregnancy in microbicide trials have been common, despite advice to avoid pregnancy and facilitated access to contraception. Outside of clinical trials, parity rates remain high in many areas hardest hit by the HIV/AIDS epidemic, even in the presence of country-wide family planning initiatives.

Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry (APR) collects prospective data on outcomes of pregnancies exposed to ARV products primarily in the context of treatment for maternal HIV infection.[21] For oral tenofovir disoproxil fumarate, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increase has been detected to date. Data through 1/31/11 show 26 birth defects among 1,092 first trimester exposures (rate of 2.4%) which is not increased compared to second and third trimester exposures (13/639, 2.0%) or 3.0% background rate in the US Centers for Disease Control (CDC) Metropolitan Atlanta Congenital Defect Program. The APR estimates that it captures data on about 15% of HIV-infected women giving birth each year in the US and a very small fraction of those from other countries. Based on that estimate, well over 10,000 pregnant women have likely used oral tenofovir in pregnancy in the US alone. In addition, the APR conducts a specific review each reporting period of renal and bone abnormalities reported after *in utero* tenofovir exposure. No increased risk of these defects has been identified.

Oral Tenofovir Investigated for Use in PMTCT

In TEmAA (Tenofovir/Emtricitabine in Africa and Asia) ANRS (Agence Nationale recherché sur le sida et les hépatites virales) 12109, thirty-six HIV-infected pregnant women received two tablets of 300 mg TDF/200 mg of FTC at onset of labor followed by one tablet daily for seven days postpartum, and received an additional tablet prior to delivery if labor lasted beyond 12 hours.[22] Women also received zidovudine 300 mg twice a day from 28 weeks to delivery as well as a single dose of nevirapine (200 mg) at onset of labor. Infants received 13 mg/kg of tenofovir oral syrup and 2 mg/kg of oral emtricitabine syrup within 12 hours of birth as well as 2 mg/kg of nevirapine syrup as a single dose on the first day of life and zidovudine syrup 4 mg/kg every 12 hours for seven days. Both maternal and neonatal tenofovir exposure were well-tolerated with lower rates of serious adverse events (SAE) than seen in a prior cohort study in the same populations.

Several other trials have examined the safety of oral tenofovir in pregnancy. Nurutdinova et al reported on 15 HIV-infected pregnant women treated for a median 127 days with tenofovir along with other oral ARV drugs. Oral tenofovir was well-tolerated by all pregnant women and infant outcomes were normal.[23] A randomized trial of a single dose of 300 mg TDF with 200 mg FTC in labor versus no therapy to reduce nevirapine resistance found no difference in adverse events (AEs) in women or infants between 200 women who received TDF/FTC and 199 with no additional therapy.[24] In a study of pharmacokinetics (PK) and safety among 19 women being treated with tenofovir during pregnancy, tenofovir was well-tolerated. Maternal area under the curve was lower than in the non-pregnant state, but other parameters were similar between third trimester and postpartum pharmacokinetic sampling.[25] A retrospective cohort of 76 women treated with tenofovir during pregnancy in Frankfurt, Germany found tenofovir to be well-tolerated, with no AEs seen in the infants after a median of 12 weeks of exposure in utero.[26]

Sexual Activity During Pregnancy
Pregnant women often continue sexual activity until the time of delivery and may increase sexual activity in an attempt to induce labor. In one survey of 425 women in New York, 62% of pregnant women had sexual activity in the third trimester, 41% had it in the last 2 weeks before delivery and 17% had it within 48 hours of hospital admission (survey of 425 women).[27] In another survey of 93 women in Ohio, 50% of pregnant women had sexual activity between 37 weeks and delivery.[28] In a study of timing of delivery among 200 women in Malaysia, 58% had sexual activity between 36 weeks and delivery.[29] Thus, it is realistic to expect that pregnant women continue to be at risk for sexual transmission of HIV during pregnancy.

Unplanned Sexual Activity and Unintended Pregnancy are Common
In many settings, women have limited control over sexual activity and reproductive planning. One survey of 370 US college students found that 34% of female college students report unwanted sexual activity. [30] Among 1,278 women attending family planning clinics in California, 53% of women reported physical or sexual partner violence, 19% reported pregnancy coercion and 15% reported contraceptive sabotage.[31] Findings from the National Survey of Family Growth indicate that 9.7% of US women have used emergency contraception and that about 50% of US pregnancies are unintended.[32] It is also important to acknowledge that sexual assault occurs in pregnant women as well as non-pregnant women.[33] [34]

Thus, given the potential role of TFV gel to reduce risk of HIV and HSV-2, the significance of these infections for pregnant women and infants, and overall reassuring safety data to date for ARV drugs in pregnancy, there is a need to supplement the existing data for this product in pregnancy by describing its safety with longer term use during various times in gestation.

2.2 1% Tenofovir Gel

2.2.1 Description

Tenofovir 1% gel contains 1 gm/100 mL of PMPA (9-R-2-phosphonomethoxypropyl adenine monohydrate), an acyclic nucleotide analogue with activity *in vitro* against retroviruses, including HIV-1 and HIV-2, as well as hepadnaviruses.[35] Further information is available in the current version of the TFV gel investigator's brochure.

2.2.2 Mechanism of Action

Tenofovir is an acyclic nucleotide analogue of adenosine monophosphate.[35] Tenofovir requires subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

2.2.3 Dose of Study Product

The dose of the TFV gel will be the concentration (1%) and volume (4 mL) previously tested in HIV Prevention Trials Network (HPTN) 050 (Investigational New Drug (IND) 55,690), CONRAD A04-095 (IND 73,382) and A04-099 (IND 73,382), HPTN 059 (IND 55,690), MTN-001 (IND 55,690), MTN-002 (IND 55,690), VOICE (MTN-003) (IND 55,690), RMP-02/MTN-006 (IND 73,382), MTN-007 (IND 73,382), MTN-008 (IND 55,690) and CAPRISA 004 (non-IND). The 4 mL application in this study delivers 40 mg of TFV to the vaginal compartment.

2.3 Universal HEC Placebo Gel

2.4.1 Description

Universal HEC Placebo gel is a vaginal product which contains hydroxyethylcellulose (HEC) as the thickener, purified water, sodium chloride, sorbic acid and sodium hydroxide.[36] Hydroxyethylcellulose is used to approximate the viscosity of other microbicide gel candidates.

2.3.1 Mechanism of Action

Universal HEC Placebo gel is designed to be inactive in the vagina. The gel is isotonic and formulated at a pH of 4.4 to avoid disrupting the normal vaginal pH and has minimal buffering capacity to avoid the inactivation of sexually transmitted pathogens.

2.3.2 Volume of Study Product

Each pre-filled applicator delivers approximately 4 mL of Universal HEC Placebo gel.

2.4 *In vitro* and Condom Compatibility Studies of Tenofovir Gel

2.4.2 *In vitro* Studies of 1% Tenofovir Gel

An assessment of TFV gel formulation included osmolality, viscosity, *in vitro* release, and permeability testing. Safety was evaluated by measuring the effect on the viability of vaginal flora, PBMCs, epithelial cells, and ectocervical and colorectal explant tissues. For efficacy testing, PBMCs were cultured with TFV or vehicle control gels and HIV-1 representing subtypes A, B, and C. Additionally, polarized ectocervical and colorectal explant cultures were treated apically with either gel. Tenofovir was added basolaterally to simulate systemic application. All tissues were challenged with HIV-1 applied apically. Infection was assessed by measuring p24 by ELISA on collected supernatants and immunohistochemistry for ectocervical explants. Formulation testing showed the TFV and vehicle control gels were >10 times isosmolar. Permeability through ectocervical tissue was variable, but in all cases the receptor compartment drug concentration reached levels that inhibit HIV-1 infection *in vitro*. The gels were non-toxic toward vaginal flora, PBMCs (peripheral blood mononuclear cells), or epithelial cells. A transient reduction in epithelial monolayer integrity and epithelial fracture for ectocervical and colorectal explants was noted and likely due to the hyperosmolar

nature of the formulation. Tenofovir gel prevented HIV-1 infection of PBMCs regardless of HIV-1 subtype. Topical and systemic tenofovir were effective at preventing HIV-1 infection of explant cultures. In addition, recent in vitro studies showed that the concentration achieved intravaginally with a 1% tenofovir topical gel has direct antiherpetic activity.[20] Tenofovir inhibited the replication of HSV clinical isolates in human embryonic fibroblasts, keratinocytes, and organotypic epithelial 3D rafts, decreased HSV replication in human lymphoid and cervicovaginal tissues ex vivo, and delayed HSV-induced lesions and death in topically treated HSV-infected mice. The active tenofovir metabolite inhibited HSV DNA-polymerase and HIV reverse-transcriptase.

2.4.3 Condom Compatibility Studies

The compatibility of 1% TFV gel was also tested with lubricated male latex condoms. A matched placebo gel and HEC placebo gel were used as comparator gels. The condoms tested were representatives of leading brands on the US market (Trojan® and Durex®) with either silicone or aqueous lubricant. The airburst test was used to evaluate changes in film integrity (strength) and test specimens were measured before and after treatment with the gels to assess changes in strength properties following the application of the three gel preparations. All three gels were shown to be compatible with the above condoms. The two application treatments of 1% TFV gel and matched placebo gel increased airburst volumes by 5 – 6 L compared with the baseline, and decreased airburst pressures by 0.2 kPa, implying a physical change to a more elastic condom. This slight change in physical properties suggests an interaction of the 1% TFV gel with the silicone lubricant, but does not indicate that the condoms are unsuitable for use in clinical studies.

2.2 *In vitro* and Condom Compatibility Studies of Placebo Gel

2.5.1 In vitro Studies of HEC-based Placebo Gel

Dilutions of the HEC gel in culture medium exhibited negligible toxicity to human vaginal epithelial cells [standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay], even at the lowest dilution tested (1:2).[8] Exposure of human vaginal epithelial cells to the HEC gel resulted in minimal IL-1α induction, even at the lowest dilutions tested (lowest dilution, 1:2).

Analyses of pH (HEC gel mixed with human seminal plasma, 8.03 ±0.26) found that a HEC formulation did not show significant buffering capacity and could not acidify the alkaline pH of seminal plasma, a favorable property for a placebo formulation.[37] *In vitro* assessments of spermicidal activity utilizing human semen from healthy donors showed that HEC gel had no significant deleterious effects on sperm motility, even after 60-minute incubation.

2.5.2 Condom Compatibility Studies of HEC-based Placebo Gel

The effects of HEC-based placebo gel on three brands of condoms including Trojan Enz®, Durex® and Trojan Supra® have been evaluated.[8] The physical properties of the three types were not significantly affected. Although there were slight increases in airburst volume for all types, and increase in pressure for synthetic condoms following gel exposure, this was considered normal and not statistically significant.

2.6 Animal Studies

2.6.1 Animal Studies of Tenofovir and 1% Tenofovir Gel

Toxicology

Tenofovir and TDF administered orally in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) ≥ 6 fold those observed in humans caused bone toxicity. In monkeys bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in some monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Four gravid rhesus monkeys were administered tenofovir subcutaneously once daily from 20 to 150 days of gestation (30 mg/kg; term: 165 ± 10 days). Fetuses were monitored sonographically, and maternal and fetal blood and urine samples were collected to assess hematologic parameters, clinical chemistry, insulin-like growth factor (IGF) levels, and bone biomarkers. Fetuses were delivered by hysterotomy near term for necropsy and evaluation of bone-related mechanical properties. Results of these studies showed 1) normal fetal development, although overall body weights and crown-rump lengths were less than those for age-matched controls ($P \leq .03$); 2) a significant reduction in circulating IGF-I ($P < .001$); 3) a small reduction in fetal bone porosity ($P \leq .03$); and 4) transient alterations in maternal body weights and bone-related biomarkers during treatment. Results of these studies suggest that chronic fetal exposure to subcutaneous tenofovir at the maternal dose of 30 mg/kg throughout gestation can alter select fetal parameters and transiently affect maternal bone biomarkers.

Evidence of renal toxicity from oral TDF was noted in four animal species. Increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 16 times (mice) and five times (rats) those observed in humans at the therapeutic dose for HIV infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that observed in humans. In rats, the study was negative for carcinogenic findings at exposures up to five times that observed in humans at the therapeutic dose. TDF was mutagenic in the *in vitro* mouse lymphoma

assay, but negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, TDF was negative when administered to male mice.

Reproductive Toxicity

There were no effects on fertility, mating performance or early embryonic development when TDF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating, and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats. Reproduction studies performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons revealed no evidence of impaired fertility or fetal harm due to tenofovir. Subcutaneous administration of TDF to pregnant rhesus macaques resulted in a fetal/maternal concentration of 60%, demonstrating that TDF does cross the placenta. Studies in rats have shown that tenofovir passes into breast milk.

Effectiveness

Adult male rhesus macaques were inoculated intra-rectally once weekly for 14 weeks (or until they became infected) with $SHIV_{SF162P3}$ at 10 median tissue culture infective doses (3.8×10^5 virus particles) that were approximately five-fold higher than the HIV-1 RNA levels noted in human semen during acute infection. Of the 12 macaques studied, four received oral TDF daily, four received oral TDF once weekly, and four control animals received no TDF. The control animals became infected after receiving a median of 1.5 virus inoculations; macaques receiving TDF daily and those receiving TDF weekly became infected after a median duration of 6.0 and 7.0 weeks, respectively. The animals continued to receive TDF after infection. One macaque in the daily TDF group remained uninfected after 14 weekly inoculations of virus. The K65R mutation was not detected in viral sequences from the infected animals through 31 weeks of the study. Although infection was delayed in treated macaques, compared with control macaques, the differences were not statistically significant (P = .315); however, the study was limited by the small numbers of animals evaluated and the variability in blood TDF levels that resulted from oral dosing. These data demonstrate that treatment with oral TDF provided partial protection against SHIV infection but ultimately did not protect all TDF treated animals against multiple virus challenges.

2.6.2 Animal Studies of HEC and Placebo Gel

Hydroxyethylcellulose is a thickening agent in Universal HEC Placebo Gel. Up to 55 intravenous injections of HEC were given to dogs (dose and number not specified) without causing injury other than that typical of the other water-soluble cellulose ethers. [8] Only transitory changes in the blood picture and the deposition of the material on the intima of the blood vessels were noted. Groups of rats maintained for two years on diets containing HEC (n not specified, up to 5%) did not exhibit any adverse effects.[8] HEC has also been administered to rats in single oral doses as high as 23,000 mg/kg without observed toxic effects (n not specified).

Intraperitoneal administration of unformulated HEC to pregnant mice in a 1% and 4% concentration caused an increase in resorptions, but no detectable increase in birth defects.[38] While no epidemiological studies of congenital anomalies in infants born to females exposed to HEC during pregnancy have been reported, the Teratogen Information System (TERIS) considers the magnitude of teratogenic risk to a child born after exposure during gestation to be none.[21]

Placebo Gel

CF-1 mice (n not specified) pretreated with medroxyprogesterone acetate were administered 0.02 mL of HEC gel vaginally, followed by a 0.01 mL inoculum of 10 intravaginal $dose_{50}$ units of HSV-2 0.3 minutes later. [39] On day 3, vaginal lavage was cultured on human foreskin fibroblasts, and mice were considered infected if a cytopathic effect was observed after 3 days of incubation. Control animals were treated similarly but were not administered the test article. Infection rate following pretreatment with HEC gel (90%) was not significantly different from pretreatment with PBS (80%) or from mice given no treatment (% not specified). HEC gel did not enhance susceptibility of mice to HSV-2 when administered 12 hours before vaginal challenge. [8]

A 10-day rabbit vaginal irritation study (10/arm, 2 arms, HEC gel vs. 0.9% saline control) found that the HEC gel was not irritating to the vaginal mucosa of rabbits when dosed daily for 10 days. One animal in the HEC gel group had an instance of vaginal redness (compared to four animals in the saline group), which did not persist and was not evident at the end of the study. Diarrhea, few feces, and soiling of the anogenital area were noted in that animal. Body weight changes were noted to be normal. In 9 of 10 animals, necropsy results were normal. Anogenital soiling was observed in the animal that exhibited erythema during the in-life phase of the study. Histopathological changes observed were similar to those seen in the control group and likely attributable to those that occur as a result of the repeated insertion of a catheter, rather than due to any effect of the test samples.

The effect of the placebo gel on vaginal transmission of $SHIV_{162p3}$ (10^3 $TCID_{50}$) to rhesus monkeys (n = 5, n = 3, respectively) was determined in two separate studies.[8] Macaques pretreated with medroxyprogesterone acetate were vaginally administered 1 mL of the HEC gel formulation 15 minutes prior to challenge with 0.5 mL $SHIV_{162p3}$. Investigators monitored total RNA load in the animal plasma for a total of 8 weeks by means of a standard quantitative RT-PCR (reverse transcriptase-polymerase chain reaction). The first study utilized the HEC gel formulation at pH 6.5; the second study utilized a formulation at pH 4.4. In both studies, all monkeys were infected, as determined by the presence of viral RNA in circulating blood, regardless of the pH of the formulation.

2.7 Clinical Studies

2.7.1 Clinical Studies of 1% Tenofovir Gel

Pharmacokinetics

A Phase 1 Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel (HPTN 050) is a completed study of TFV vaginal gel with published data. Eighty-four (60 HIV negative and 24 HIV-positive) women applied either 0.3% or 1% TFV gel once or twice daily for 14 days. Pharmacokinetic evaluations were performed in 25 women. Systemic absorption was limited (maximum serum levels 3.0-25.8 ng/mL) and levels were below the limit of detection in 11/25 participants.

A study of the PK of TFV gel was conducted among 49 sexually-abstinent women in the USA and Dominican Republic (CONRAD A04-095, IND 73,382).[40] The following are results from a subset (n = 21) who completed the single-dose phase. Following an intravaginal dose (4 g) of TFV gel, blood samples were obtained at 0.5, 1, 2, 4, 6, 8, and 24 hr(s) from all participants. Participants were randomized to one of seven time-points [0.5, 1, 2, 4, 6, 8, and 24 hr(s)] for vaginal fluid collection and vaginal biopsies. Total TFV was measured in blood plasma, fluid, and biopsies. Most blood plasma TFV concentrations were below 5 ng/mL. Four had higher values (up to 19.5 ng/mL) which were not sustained. Vaginal fluid concentrations were high, generally 1.5-5.0 x 10^6 ng/mL through 8 hrs and 4.5-47.1 x 10^4 ng/mL at 24 hrs. The mean concentration in vaginal tissue at 0.5, 1, 2, 4, 6, 8 and 24 hr(s) were 275 x 10^3, 450 x 10^3, 186 x 10^3, 89 x 10^3, 69 x 10^3, 24 x 10^3 and 15 x 10^3 ng/g of tissue, respectively, (lower limit of quantitation [LLOQ] = 1 ng/mL) with a peak at 1-4 hrs. Vaginal fluid elimination appeared linear. Tissue elimination appeared to follow a multi-compartment model. Total TFV was detectable in vaginal tissue and fluid up to 24 hrs post single-dose exposure.

MTN-001 was a Phase 2 study of adherence to, and pharmacokinetics of, oral and vaginal preparations of tenofovir among 144 sexually-active HIV-negative women at sites in Uganda, South Africa and the United States, who were assigned to follow each regimen for six weeks, with one week between when no study product was used.[41-43] Concentrations of tenofovir in vaginal tissue and blood were found to be 2,352 fmol (femtomols) of TFV-PP per mg of vaginal tissue after 1% TFV gel use, whereas, with TDF 300 mg tablet, the concentration in tissue was less than 17 fmol/mg. The concentration of TDF-PP in PBMC associated with oral TDF use was 52 fmol/million cells and less than 5 fmol/million cells with the vaginal gel. Rates of genital symptoms did not differ significantly by regimen (vaginal 21%, dual 21%, oral 18%).

Safety

In HPTN 050, the 1% TFV gel formulation was well tolerated in both HIV-uninfected and infected women. Ninety-two percent reported at least one AE. The majority of these events were mild (87%) and limited to the genitourinary tract (77%). The five most reported mild genital AEs were pruritus (n = 18), erythema (n = 14), petechial/ecchymosis (n = 14), vaginal discharge (n = 13), and burning (n = 10). Four

severe AEs were reported, but only one (lower abdominal pain) was thought to be product-related. Product concentration, sexual activity and HIV status were not associated with a specific AE pattern. No clinically significant systemic toxicity was observed. No SAEs were reported.

In MTN-001, all three daily regimens (1% TFV vaginal gel, oral tablet and the two combined) were found to be safe and well-tolerated. Nausea occurred in 15 percent of the women when using the tablet and 14 percent when the gel and tablet were used together. Vaginal itching and irritation were the most common side effects with the gel.

In a male tolerance study (CONRAD A04-099/IND 73,382), 1% TFV gel was well tolerated in men following seven days of once daily penile exposure.[44] There were few genital findings observed after product use and all findings were classified as mild, small in size and requiring no treatment. Reported symptoms were mild, of short duration and resolved by the final visit. There were no noticeable differences between signs and symptoms of genital irritation in the circumcised compared to uncircumcised group.

HPTN 059 was a Phase 2 four-arm, three-site, randomized, controlled trial comparing 1% TFV gel used once daily and gel used prior to intercourse, to placebo gel, with 6 months gel exposure and follow-up.[45] 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 between ages 18 and 50, but not menopausal or post-menopausal. Participants had six months of study gel exposure and six months of follow-up. They were randomized to either a once-daily or coitally-dependent group, and received either TFV or placebo gel. No statistically significant differences were seen between those receiving active and placebo gels in complete blood count, liver function tests, or renal function tests. At the Week 24 Visit, no participants had exam findings suggestive of vaginitis, cervicitis, superficial disruption, disrupted blood vessels, or intermenstrual bleeding. Adherence to study gel was high, and was supported by pharmacokinetic (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.

The CAPRISA 004 trial was a Phase 2B trial which was designed to assess the effectiveness and safety of a TFV 1% vaginal gel, for the prevention of HIV acquisition in females.[1] A double-blind, randomized controlled trial was conducted comparing TFV gel (n = 445) with placebo gel (n = 444) when used in a pericoital regimen, in sexually active, HIV-uninfected 18 to 40 year-old females 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. No increase in the overall adverse event rates was observed. Although TFV gel was associated with mild diarrhea, no significant safety concerns were seen.

Pregnancy Outcomes

MTN-002 was a Phase 1, single-dose, open-label, safety study of 1% TFV gel in term pregnancy.[46] Sixteen healthy, HIV-negative women with uncomplicated pregnancy at

term undergoing planned cesarean delivery received a single dose of gel prior to delivery. Maternal serum drug concentrations were collected over 24 hours, specimens of amniotic fluid, cord blood, placental and endometrial tissue were collected during surgery, and maternal/neonatal AEs were tabulated. All 16 women had detectable serum TFV concentrations and 15 (93.8%) of 16 infants had detectable concentrations in cord blood. The median maternal C_{max} and fetal cord blood TFV concentrations were 4.3 and 1.9 ng/ml respectively. Median tissue TFV concentrations were similar to maternal serum TFV concentrations and median tenofovir diphosphate concentrations were below the limit of quantification. No AEs were related to TFV gel exposure. Single application of TFV gel in term pregnancy produces very low serum and tissue concentrations that are consistent with concentrations in non-pregnant women. Fetal exposure after vaginal dosing is also low. These findings supported further investigation of TFV gel in pregnancy.

Within CAPRISA 004, the overall pregnancy rate was 4.0 per 100 woman-years, with 3.2 pregnancies per 100 woman-years in the TFV arm and 4.7 per 100 woman-years in the placebo arm (P = 0.183). At the time of CAPRISA 004 analysis, there were six ongoing pregnancies while 58.3% of the remaining 48 pregnancies had resulted in a full-term live birth. There were no significant differences in pregnancy outcomes by study arm and there were no congenital anomalies. A total of 20.9 w-y of follow-up occurred while women were not using gel due to pregnancy.

MTN-008 is an expanded safety study of 1% TFV gel during pregnancy and breastfeeding at two US sites. In the Pregnancy Cohort, women at term gestation use TFV gel or placebo gel vaginally on a daily basis for one week, with safety monitoring and PK assessments performed throughout dosing and follow-up. Provided that no safety concerns are identified in this first group, a second group of women at near term gestation will enroll for the same schedule of gel dosing and follow-up. In the Lactation Cohort, mothers and their infants (about 1 to 6 months old) will enroll for one week of open-label maternal dosing of 1% TFV gel. Safety assessments will occur for both mothers and babies, with tenofovir levels checked in maternal blood, infant blood (via heel stick), and mothers' breast milk.

Pregnancy registry (MTN-016) data for VOICE participants with first trimester exposure to study gel (TFV and placebo gel) are reviewed at least annually by the MTN Study Monitoring Committee, and to date have triggered no serious safety concerns. The mean duration of estimated gel exposure in VOICE at time of pregnancy diagnosis is currently 15 days. Outcomes from MTN-016 will be unblinded when VOICE is unblinded (projected late 2012). In addition, the MTN Study Monitoring Committee (SMC) will review data from the Pregnancy Cohort in MTN-008.

Resistance

In HPTN 050, no new resistance mutations evolved in plasma or cervicovaginal lavage after 14 days of TFV gel use among 22 HIV-positive women, although 3 women had plasma mutations associated with low level tenofovir resistance identified at both Days 0 and 14 (M41L, L210M, ±T215I/Y).

Effectiveness for Prevention of HIV and HSV-2

The CAPRISA 004 trial was a Phase 2B trial which was designed to assess the effectiveness and safety of a 1% TFV vaginal gel, for the prevention of HIV acquisition in women. A double-blind, randomized controlled trial was conducted comparing TFV 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 TFV 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 differences in the overall adverse event rates were observed. The use of TFV gel was associated with 51% protection against HSV-2 (CI: 22% - 70%).

2.7.2 Clinical Studies of Placebo Gel

Unformulated HEC is known to be a non-irritating substance in humans (skin sensitization is unusual), with doses less than 2 gm/kg by ingestion not expected to be toxic.[47] No inhalation studies have been conducted, but exposure of humans to the dust in manufacturing operations over many years has not led to any known AEs. The HEC placebo formulation was developed and adopted for use in HPTN 035 (IND 62,366), the Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides Buffer Gel and 0.5% PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women.

A randomized, closed label, Phase 1 study of daily vaginal HEC gel exposure was conducted in 2003.[48] Thirty females were randomized to twice-daily vaginal applications of 3.5 mL of HEC gel or polystyrene sulfonate (PSS) vehicle. The primary objective of this study was to assess and compare the gels' effects on symptoms and signs of irritation of the external genitalia, cervix, and vagina as seen on naked eye exam after 7 and 14 days of use including disruption as seen on colposcopy after 14 days of use. Both gels appeared safe for use twice a day for 14 days in sexually abstinent women. Two of 14 women (14.3%) randomized to the PSS placebo gel reported at least one symptom of mild genital irritation, which included genital burning, soreness and pelvic pain. A lower proportion of women in the HEC group experienced any evidence (signs and/or symptoms) of genital irritation. No deep genital disruption was observed in either product group. Minimal changes in wet mounts, pH, Nugent scores, neutrophils, and vaginal flora were observed in both product groups. A pilot study to optimize trial procedures for a proposed Microbicides Development Programme placebo-controlled trial utilized the same Universal HEC Placebo gel as the study gel; no serious adverse product related events were reported.[8]

Multiple studies, including MTN-003/VOICE, RMP-02/MTN-006, MTN-007, MTN-008, and CAPRISA 004 have used HEC-based gel as the placebo gel, with no significant safety issues noted. VOICE alone will constitute approximately 1,800 p-y of follow-up among approximately 1,000 women in the HEC placebo gel arm. Both HPTN 035 and

CAPRISA 004 had pregnancies occur among participants assigned to HEC placebo gel. Neither trial reported a difference in pregnancy outcomes between those assigned to active and those assigned to placebo gel. In addition, HPTN 035 did not report a difference in pregnancy outcomes between the HEC placebo gel group and the no gel group.

2.7.3 Data on Oral Tenofovir in Pregnancy

The oral formulation of tenofovir (tenofovir disoproxil fumarate) is not a study product in MTN-019. However, information related to the safety of oral tenofovir in pregnancy is included here for background information.

Tenofovir/Emtricitabine in Africa and Asia (TEmAA)
The TEmAA study investigated the use of oral TDF and FTC as a possible alternative or complement to single dose NVP for prevention of mother-to-child transmission. The objectives of TEmAA were to study the PK properties, safety and viral resistance pattern of the combination of oral TDF (600 mg) and FTC (400 mg) in HIV-1-infected pregnant women and their newborns, with a view to prevention of mother-to-child transmission of HIV-1 in Africa and Asia. It is a Phase 2, multisite, open-label trial conducted in two steps with 30 mother-infant pairs per step and with a balanced allocation in Abidjan (Côte d'Ivoire), Soweto (South Africa) and Phnom Penh (Cambodia).

Step 1 of TEmAA was administration of oral TDF/FTC to the mother and Step 2 was administration of oral TDF/FTC to the mother and the newborn. In TEmAA Step 2, median tenofovir and emtricitabine breast milk doses represented 0.03% and 2% of the proposed oral infant doses. Neonatal simulated plasma concentrations were extremely low for tenofovir but between half maximal inhibitory concentration and adult minimal concentration for emtricitabine. It was noted that the rare children who will acquire HIV despite TDF/FTC therapy will need to be monitored for viral resistance acquisition. Clear and significant safety concerns were not identified among infants exposed *in utero*, although it was noted that some infants with AEs had a higher intracellular concentration of emtricitabine.

HPTN 057
The purpose of HPTN 057 is to evaluate the safety and PK of TDF when administered to HIV-infected pregnant women during labor and to their infants during the first week of life to determine the optimal regimen for a subsequent efficacy trial, if indicated. This study is a Phase I, open label, non-controlled trial. Eligible women and their infants were enrolled in one of four cohorts outlined below. Cohort 4 was added after reviewing the pharmacokinetic and safety data from Cohorts 1 and 3. In Cohort 1, mothers receive a single 600 mg oral dose of TDF at onset of labor; infants are not dosed. In Cohort 2, mothers are not dosed; infants receive 4 mg/kg of the TDF oral suspension at birth (within 12 hours) and on Days 3 and 5 of life. In Cohort 3, mothers receive a single 900 mg oral dose of TDF at onset of labor and infants receive 6 mg/kg of the TDF oral suspension at birth (within 12 hours) and on Days 3 and 5 of life. Cohort 4 mothers

receive a single 600 mg oral dose of TDF at onset of labor and infants receive 6 mg/kg of the TDF oral suspension daily for 7 days initiated at birth.

The primary objectives of HPTN 057 are the following:

- To evaluate the safety and tolerance of intrapartum/neonatal TDF in HIV-infected women and their infants; and
- To evaluate the pharmacokinetics of intrapartum/neonatal TDF in HIV-infected women and their infants and to determine maternal plasma exposure with single doses of 600 mg and, if necessary, 900 mg.

One of the secondary objectives is to measure TDF concentration in amniotic fluid and breast milk following maternal exposure to intrapartum TDF.

A total of 53 mother-infant pairs divided into two cohorts have been evaluated in this study in Malawi and Brazil. In Cohort 1, maternal PK sampling for TDF plasma concentration occurred pre-dosing and at 1, 2, 4, 8, 12, 18-24, and 36-48 hours post-dosing. Cord blood was collected once, as well as infant blood for PK at 4, 12, 18-24, and 36-48 hours after birth. The mothers in this cohort delivered at median of 2.9 hours after dosing. Amniotic fluid samples were also collected from women who delivered via cesarean delivery at a median of 4.1 hours after dosing (n = 5). Data from Cohort 1 are presented in Tables 1 and 2 below.

Table 1: Median (range) of Maternal Tenofovir Levels in HPTN 057 (Cohort 1)

	Pregnant women, 600 mg (n = 30)	**Non-pregnant adults, 600 mg**
T_{max} (hr)	1.0 (1.0-8.0)	1.5
C_{max} (ng/mL)	448 (110-928)	573
AUC (ng*hr/mL)	4221 (2767-24459)	4389
$T_{1/2}$ (hrs)	19.5 (11.1-32.8)	11.9

Table 2: Tenofovir Concentrations in Breast Milk in HPTN 057 (Cohort 1)

Day Collected	**#**	**Number with Detectable Tenofovir (conc [ng/mL])**
1	1	1 (17.8)
2	3	2 (106,6.3)
4-6	21	1 (15.7)
41-44	13	0
79-89	21	0

Mirochnick examined HPTN 057 PK of TDF after single-dose administration to HIV-1 infected mothers; mothers and infants were followed for safety and tolerance. Of the 53 mother-infant pairs enrolled, breast milk was collected from 25 breastfeeding mothers who received a single 600 mg dose of TDF tablets at onset of labor or 4 hrs prior to cesarean delivery. Tenofovir was detectable in 4/25 (16%) breast milk samples collected during the infants' first week of life with concentration of 13 (6-18) ng/mL. It is unclear from the limited data set the extent of infant tenofovir exposure during breastfeeding with chronic maternal tenofovir dosing.

In Cohort 2, newborns received TDF 4 mg/kg as soon as possible after birth and on Days 3 and 5. PK sampling was done on Day 0 (cord blood, pre-dose and 2, 10 and 18-24 hours post-dose) and on Days 3 and 5 (at pre-dose, 2, 10, 18-24 and 36-48 hours post-dose). Results from Cohort 2 show that infant plasma tenofovir concentrations were greater at Day 0 than on Days 3 or 5 (Table 3). The infant dosing schedule, however, did not maintain infant plasma tenofovir concentrations above 50 ng/mL, during the first week of life.

Table 3: Median (range) Tenofovir Concentrations in Infants (Cohort 2)

Day of Dose	0 n = 23	3 n = 21	5 n = 21	Adults 300 mg qd
T_{max} (hr)	2.0 (1.6-10.0)	2.1 (1.9-43.9)	2.0 (1.8-18.0)	2.0
C_{max} (ng/mL)	200 (66-428)	78 (27-363)	87 (22-252)	375
AUC (ng*hr/mL)	4013 (2003-8874)	2365 (728-8000)	1631 (884-4317)	3179
$T_{1/2}$ (hrs)	21.6 (16.0-124.5)	19.5 (6.8-44.0)	18.1 (5.2-61.3)	11.7
Cl/F (mL/kg/hr)	69 (134-1808)	1375 (566-3425)	1713 (451-3562)	584

Pediatric HIV/AIDS Cohort Study (PHACS)

The PHACS Surveillance Monitoring of Antiretroviral Toxicity (SMARTT) study enrolls HIV-exposed uninfected children in the US with annual follow-up to examine potential adverse effects of *in utero* ARV exposure.[49] In 2010, PHACS evaluated the association of oral TDF exposure during pregnancy with low birth weight (LBW, < 2.5 kg) and infant growth at 1 year of age based on z-scores less than -1.5 for length, weight, and head circumference (HC). Logistic regression models for LBW and growth outcomes were fit, adjusting for demographic and socioeconomic characteristics, maternal health status (CD4 < 250, viral load > 1000 copies/mL) and substance use during pregnancy. 1855 children were enrolled in the SMARTT study as of February 2010 and had ARV information available. 380 (20%) were exposed *in utero* to TDF, increasing from 15% in 2003 to 38% in 2009. There was no increased risk of LBW for infants exposed vs. unexposed to TDF (21.2% vs. 19.5%, $P = 0.46$), and there remained no TDF effect after adjustment for highly active antiretroviral therapy and other factors (adjusted odds ratio (AOR) = 1.03, 95% CI: 0.81, 1.48, $P = 0.56$). However, among 470 1-year olds, those exposed *in utero* to oral TDF had marginally increased risk of low length and weight z-scores, while 1st trimester oral TDF exposure was associated with significantly increased risk of low HC z-score (AOR = 2.48, 95% CI = 1.17, 5.27, $P = 0.02$). While oral TDF use during pregnancy does not appear to increase the risk for low birth weight, it is possible that exposure may slow infant growth. It was concluded that further infant follow-up studies are warranted for monitoring the safety of oral TDF exposure during pregnancy.

2.8 Study Hypotheses and Rationale for Study Design

2.8.1` Study Hypotheses

It is hypothesized that 1% TFV gel used daily for up to 4 weeks during pregnancy will be safe and well-tolerated.

2.8.2 Rationale for Study Design

The study groups in MTN-019 are based on the gestational age at onset of dosing, not the total dosing period, enabling data to be collected across a wide span of gestational ages. The combination of gestational age groups and the scheduled dosing period of 28 days will maximize coverage and avoid "gaps" throughout the second and third trimesters. Thus, Group 1 does not include onset of dosing at gestational ages later than 37 6/7 weeks, because normal term delivery could reasonably be expected to shorten the dosing period significantly for many participants, if dosing were initiated then. The protocol has minimized risk by taking a carefully monitored, step-wise approach to dosing starting at later gestational ages, then progressing earlier in pregnancy once safety is confirmed. This protocol also provides a unique opportunity to better describe the PK and adherence profiles associated with longer term use of tenofovir gel in pregnancy. In the event that the VOICE study finds daily use of TFV gel safe and effective for prevention of HIV among women, the MTN-019 team would give serious consideration to the omission of the placebo arm in this trial.

Safety

The four-week scheduled dosing period in MTN-019 follows a step-wise approach to the investigation of TFV gel exposure during pregnancy, and will provide important late first trimester and second trimester safety data not obtained in other studies of tenofovir gel. Table 1 below shows that the majority of data on TFV gel in pregnancy is in the first and third trimesters. MTN-019 will provide necessary information on the safety of TFV gel, by evaluating pregnancy outcomes as well as describing the possible impact of TFV gel on the vaginal microenvironment, an important area for investigation, due to the potential for disruptions in normal vaginal ecology to impact gestational age at delivery and risk for neonatal infection.

Table 4: Pregnancy Data on 1% TFV Gel by Trimester

	MTN-002 IND 55,690	CAPRISA 004 Non-IND	MTN-016 Non-IND	MTN-003 IND 55,690	MTN-008 IND 55,690	MTN-019 IND 55,690	MTN-018C IND 55,690
First trimester		Unscheduled multi-dose exposure, placebo controlled, with product hold at diagnosis of pregnancy	Registry data obtained from VOICE participants	Unscheduled multi-dose exposure, placebo-controlled, with product hold at diagnosis of pregnancy		Late first trimester only	Planned exposure of multi-dose, open-label TFV gel, pending VOICE results
Second trimester						28-day exposure, placebo controlled	Planned exposure of multi-dose, open-label TFV gel, pending VOICE results
Third trimester	Planned single-dose, open-label TFV gel at term		Registry data obtained from MTN-002 and MTN-008 participants		7-day exposure, placebo-controlled, at term and near term	28-day exposure, placebo-controlled	Planned exposure of multi-dose, open-label TFV gel, pending VOICE results

The grading cut-offs for primary safety endpoints were selected with the intent of detecting potential safety signals and tolerability issues that could potentially be 1)

clinically significant and specific to pregnancy, e.g., post-partum hemorrhage; 2) more common in the pregnant than non-pregnant state, e.g., increased vaginal discharge; and 3) appropriate for the next stage of evaluation in pregnancy, i.e., closer to real-world use than a single-dose Phase 1 trial, which would typically capture all potential AEs of all grades.

Pharmacokinetics
The PK objective is to establish the peak blood concentration and the time course over approximately the first 6 hours after a vaginal dose of TFV under steady-state vaginal dosing conditions. This will be accomplished using a sparse sampling method in which all subjects will contribute one pre-dose and one post-dose (1-3 hours, 3-5 hours, or 5-7 hours) blood sample for TFV concentration analysis. Using sparse sampling methods, the peak concentration (C_{max}) and trough concentration (C_{tau}) will be assessed. This data will then be analyzed for differences among gestational groups within the study. In addition, the study participants will be compared to an external historical control using similar data from MTN-001.

Adherence
Recent findings from the iPrEx and CAPRISA 004 trials highlight the critical connection between drug adherence and level of protection from HIV infection.[1, 50] It is currently unknown what impact pregnancy may have on a woman's incentive or ability to adhere to a daily regimen of TFV gel. The first trial of repeat dosing of tenofovir gel in pregnancy is currently underway (MTN-008), but the prescribed length of dosing is brief (7 days). MTN-019 will be the first trial to provide data on adherence to tenofovir gel during pregnancy over a longer period of use (28 days). As all trials of prescribed use of antiretroviral drugs during known pregnancy have been in the context of treatment for HIV/AIDS and/or PMTCT, it is impossible to extrapolate rates of adherence from those trials to the context of HIV prevention. Arguably, adherence could be higher in the pregnant than in the non-pregnant state, due to incentive to avoid HIV infection while on the brink of the greater responsibility of motherhood and/or concern for possible perinatal transmission, or lower, due to physical discomfort with inserting applicators and/or fear of adverse drug effects on the developing fetus. Women might be more or less tolerant of study products with side effects similar to those already occurring as normal discomforts of pregnancy (e.g., increased vaginal discharge). Greater attention to the mother's health and investment in the pregnancy outcome by the woman's partner and family may also impact her ability and desire to adhere. Lastly, it is acknowledged that emerging data regarding the efficacy and safety of oral and topical formulations of TFV as HIV chemoprevention may impact women's motivation to adhere to prescribed use.

2.9 Justification of Dosing

The concentration planned for MTN-019 (1% TFV gel) has previously been studied in all investigations of topical TFV in women, including both protocols examining intentional dosing during pregnancy (MTN-002 and MTN-008). Given the two dosing regimens associated with potential TFV gel licensure (coitally dependent vs. daily), the investigation of safety for daily dosing was deemed a high priority.

3 OBJECTIVES

3.1 Primary Objective

- **Safety.** To describe the safety profile of 1% tenofovir gel used daily per vagina for up to 28 days during different gestational age ranges during pregnancy

3.2 Secondary Objectives

- **Pharmacokinetics.** To establish the peak blood concentration and the time course over the first 6 hours after a vaginal dose of tenofovir under steady-state vaginal dosing conditions during pregnancy

- **Adherence.** To assess the adherence to daily use per vagina of 1% tenofovir gel for 28 days among pregnant women

3.3 Exploratory Objectives

- **Vaginal Microenvironment.** To describe vaginal microenvironment changes associated with tenofovir 1% gel used daily during different gestational age ranges during pregnancy

- **Behavior.** To describe sexual activity, condom use and intravaginal practices during different gestational age ranges of pregnancy

- **Acceptability.** To explore participant acceptability of study product use in pregnancy

- **Pharmacokinetic.** To describe maternal:cord blood ratios for those participants who deliver during study product dosing

- **Adherence.** To compare participant self-report vs. electronic monitoring of study product adherence to a daily regimen of vaginally applied 1% tenofovir gel over 28 days of use (at sites with capacity)

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-019 is a multi-site, double-blinded, two-arm, randomized, placebo-controlled trial of daily vaginal use of 1% tenofovir gel vs. Universal HEC Placebo gel (2:1, active:placebo) among pregnant women with onset of 28-day dosing period to occur within the following gestational age ranges:

Group 1: 36 0/7 weeks – 37 6/7 weeks (114 women)

Group 2: 28 0/7 weeks – 32 6/7 weeks (90 women)
Group 3: 20 0/7 weeks – 24 6/7 weeks (90 women)
Group 4: 12 0/7 weeks – 16 6/7 weeks (90 women)

The four groups will be filled sequentially.

4.2 Study Endpoints

Study endpoints are listed below.

Primary Endpoints:

- **Maternal outcomes**
    - Grade 2 or higher AEs in the following categories
        - Specific laboratory abnormalities
            - Alanine transaminase (ALT)
            - Aspartate aminotransferase (AST)
            - Creatinine
        - Specific genital/pelvic signs/symptoms
            - Dyspareunia
            - Pain (vulvar, vaginal, and/or pelvic)
            - Tenderness (vulvar, vaginal, and/or pelvic)
            - Itching (vulvar and/or vaginal)
            - Edema (vulvar, vaginal, and/or cervical)
            - Erythema (vulvar, vaginal, and/or cervical)
            - Lesions (vulvar, vaginal, and/or cervical)
            - Vulvar rash
            - Vaginal dryness
            - Dysuria
            - Vulvovaginitis
            - Cervicitis
        - Pregnancy complications
            - Genital bleeding
            - Preterm labor
            - Spontaneous preterm delivery
            - Chorioamnionitis
            - Postpartum endometritis
            - Gestational hypertension and/or pre-eclampsia
            - Gestational diabetes
            - Sepsis
            - Abruptio placentae
            - Postpartum hemorrhage
            - Premature rupture of membranes (prior to onset of labor, at term or preterm)

- For AEs not included above, Grade 3 or higher events judged by the investigator to be related to the study gel or applicator
- All serious adverse events
- Pregnancy outcomes

- **Neonatal outcomes (first 30 days of life)**
  - All serious adverse events

Secondary Endpoints

- **Pharmacokinetics**
  - Maternal blood levels of tenofovir
- **Adherence**
  - Self-reported product use captured through questionnaires
  - Study drug levels
  - Count of returned unused applicators

Exploratory Endpoints:

- **Vaginal Microenvironment**
  - Gram stained vaginal smears
  - Vaginal pH
  - Identification of vaginal microorganisms at sites approved by NL
  - Genital biomarker expression (selected by the MTN Biomedical Science Working Group) in vaginal and cervical secretions
- **Behavior**
  - Self-report via questionnaire
- **Acceptability**
  - Self-report via questionnaire
- **Pharmacokinetics**
  - Cord blood levels of tenofovir for infants of mothers who dosed within 24 hours of arriving at the hospital for delivery
- **Adherence**
  - Number of days in which the study product was used as reported electronically (at sites with capacity)

,

4.3 Description of Study Population

Participants are healthy, sexually active, HIV-uninfected women 18 to 45 years old, with singleton pregnancy, without evidence of maternal or fetal complications in the current pregnancy, and their newborn infants.

4.4 Time to Complete Accrual

An accrual period of approximately 24 months is estimated.

4.5 Study Groups

The following study groups are included in MTN-019:

Table 5: Study Groups

	Number of Participant Mothers in Each Gestational Age Range			
	Group 4	**Group 3**	**Group 2**	**Group 1**
	12 0/7 – 16 6/7 weeks	**20 0/7 – 24 6/7 weeks**	**28 0/7 – 32 6/7 weeks**	**36 0/7 – 37 6/7 weeks**
1% TFV Gel	60	60	60	76
Universal HEC Placebo Gel	30	30	30	38

4.6 Expected Duration of Participation

Duration of participation following enrollment will vary depending on gestational age at time of enrollment and length of pregnancy prior to pregnancy outcome (approximately 5 – 34 weeks). Figure 1 illustrates the increasing duration of participation for later enrolled groups, although it should be noted that the scheduled study product dosing period remains the same for all four groups.

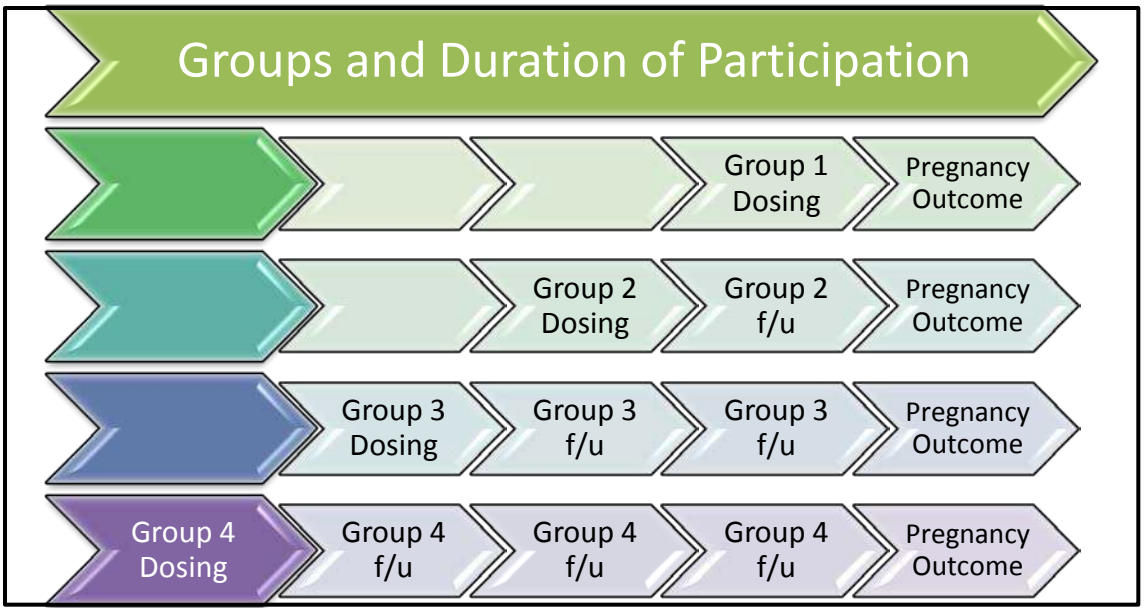


Figure 1: Groups and Expected Duration of Participation

4.7 Sites

Study sites in the US and sub-Saharan Africa are noted at www.mtnstopshiv.org.

5 STUDY POPULATION

5.1 Selection of the Study Population

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

5.1.1 Recruitment

Study site staff will recruit potential participant mothers from clinical care and other community-based site(s), including antenatal care and family planning clinics, using Institutional Review Board/Ethics Committee (IRB/EC)-approved materials. Educational/recruitment activities are permissible for Groups not yet open to accrual provided that potential participant mothers are informed that accrual into those Groups will be contingent upon satisfactory safety review for previously enrolled participants.

5.1.2 Retention

The target for retention will be 95% of enrolled women over the study period.

5.2 Inclusion Criteria

1. Age 18 through 45 years (inclusive) at screening, verified per site standard operating procedures (SOPs)

2. At enrollment, singleton, viable pregnancy of gestational age within the limits for current group for enrollment

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

4. Able and willing to provide the following:

    a. Written informed consent to be screened for and take part in the study
    b. Adequate locator information, as defined in site SOPs
    c. Adequate documentation of entry to antenatal care, as defined in site SOPs
    d. Permission to contact and provision of adequate contact information for participant's antenatal care provider
    e. Permission to obtain copies of antenatal care records

    Note: Potential participants who have not begun antenatal care are not eligible for enrollment in MTN-019. Rescreening after documented entry to antenatal care is permissible.

5. HIV-uninfected based on testing performed by study staff at screening and enrollment (per algorithm in Appendix II)

6. Per the clinical judgment of the IoR/designee at Enrollment, pelvic exam (including cervical exam) normal for estimated gestational age and parity

7. Per the clinical judgment of the IoR/designee at Enrollment, ultrasound results are complete, consistent with normal singleton intrauterine pregnancy, and provide an assessment of gestational age

    Note: Ultrasound should be obtained if results are not available or complete, according to the clinical judgment of the IoR/designee.

8. Per participant mother report, willingness by the participant mother to receive information regarding and consider participation in MTN-016, a pregnancy registry study which collects additional information on pregnancy safety and the growth and development of babies up to one year of age.

9. At screening and enrollment, agrees not to participate in other research studies involving drugs, vaccines, medical devices, or vaginal products for the duration of study participation

5.3 Exclusion Criteria

1. Participant mother reported any of the following:

    a. Prior exposure to gel or oral formulation of tenofovir (ever)
    b. Known sensitivity to any component of the study products (ever)

c. Post-exposure prophylaxis (PEP) for HIV exposure within 6 months prior to enrollment
d. Participation in any research study involving drugs, medical devices, or vaginal products during the current pregnancy
e. Non-therapeutic injection drug use in the 12 months prior to screening

2. By participant mother report, noted on antenatal record, or clinical evidence at the time of Enrollment of any of the following in the current pregnancy:
    a. Multiple gestation
    b. Placenta previa
    c. Cervical cerclage
    d. Abnormal fetal anatomy (in the opinion of the IoR or designee)
    e. Intrauterine growth restriction
    f. Pre-existing or gestational diabetes
    g. Hypertensive disorder of pregnancy
    h. Treatment for preterm labor

3. By participant mother report, or noted on review of medical record, any of the following in a previous pregnancy:
    a. Intrauterine growth restriction
    b. Gestational diabetes
    c. Hypertensive disorder of pregnancy
    d. Intrauterine fetal demise (estimated gestational age ≥20 weeks)
    e. Delivery prior to 37 0/7 weeks

4. By participant mother report at screening or enrollment:
    a. Intends to relocate away from the study site during the period of expected study visits
    b. Plans to travel away from the study site during the expected study product dosing period, such that travel would preclude the completion of one or more scheduled study visits
    c. Plans to deliver outside of a hospital

    Note: Plans to deliver in non-hospital setting is exclusionary due to logistical challenges related to specimen and delivery outcome data collection for out-of-hospital birth.

5. Currently breastfeeding

6. As determined by the IoR/designee, any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, including active tuberculosis, or medication use that would make study participation unsafe

    Note: While investigators have discretion to exclude participant mothers based on clinical judgment regarding concomitant medication use, there are no contraindicated medications, other than other antiretroviral drugs commonly used to treat HIV-infected persons (who are excluded from MTN-019).

7. At enrollment, clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff)

   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 site IoR/designee is considered expected and is not exclusionary.

   Note: Otherwise eligible participant mothers with exclusionary pelvic exam findings may be enrolled/randomized after the findings have improved to a non-exclusionary severity grading or resolved. If improvement to a non-exclusionary grade or resolution is documented within 42 days of providing informed consent for screening, the participant mother may be enrolled, provided she is otherwise eligible.

8. Has any of the following laboratory abnormalities: during the screening period:

   a. Hemoglobin value of Grade 3 or higher according to DAIDS Toxicity Table
   b. Platelet count less than 100,000 mm^3
   c. AST or ALT greater than 1.5 X upper limit of normal
   d. Serum creatinine greater than 1.0 mg/dL
   e. Hepatitis B surface antigen (HBsAg) positivity
   f. Urine dipstick positive for protein ≥ 2+
   g. Urine dipstick positive for glucose ≥ 2+
   h. Positive for malaria (at sites with capacity, where women are at risk and testing through antenatal care provider is not otherwise available)

   Note: Otherwise eligible participant mothers with an exclusionary test result (other than HIV or HBsAg) may be re-tested during the screening process. If a participant mother is re-tested and a non-exclusionary result is documented within 42 days of providing informed consent for screening, the participant mother may be enrolled, provided she is otherwise eligible.

9. Grade 2 or higher Pap result (e.g., high-grade squamous intraepithelial lesion)

   Note: Pap smears are conducted only at sites with capacity, where standard of care and when clinically indicated. Women with abnormal Pap smears can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology). Need for a repeat Pap smear within 6 months does not preclude enrollment prior to that result becoming available.

10. Diagnosed with a sexually transmitted infection or reproductive tract infection requiring treatment, per current CDC or World Health Organization guidelines, as applicable

    Note: Otherwise eligible participant mothers diagnosed during screening with sexually transmitted infection (STI)/reproductive tract infection (RTI) requiring treatment are 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 for screening, the participant mother may be enrolled, provided she is otherwise eligible. Asymptomatic BV and asymptomatic candidiasis do not require treatment during the screening period and are not considered exclusionary. Known positive HSV status is not exclusionary. Condyloma ≤ Grade 1 are not considered exclusionary.

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

5.4 Co-enrollment Guidelines

In general, participants should not take part in other research studies involving drugs, medical devices, or vaginal products while taking part in MTN-019. Participant mothers will be discouraged from taking part in other studies, except for the following:

- Participants may take part in ancillary or observational studies approved by MTN-019 Protocol Chairs, including MTN-016
- Participants who become infected with HIV may join observational and/or interventional studies for HIV-infected persons (e.g., MTN-015, at applicable sites)

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-019, the IoR/designee will consult the Protocol Safety Review Team (PSRT) regarding ongoing product use and other potential safety considerations associated with co-enrollment.

6 STUDY PRODUCT

6.1 Regimen

Within each study group, participant mothers will be randomized to receive 1% tenofovir gel or placebo gel in a 2:1 ratio. The study groups will be enrolled sequentially in the order noted in Table 6.

Table 6: Order of Study Groups

GROUP	GESTATION
Group 1	36 0/7 weeks – 37 6/7 weeks
Group 2	28 0/7 weeks – 32 6/7 weeks
Group 3	20 0/7 weeks – 24 6/7 weeks
Group 4	12 0/7 weeks – 16 6/7 weeks

Each participant mother will use one applicator of 1% tenofovir gel or placebo gel for approximately 28 consecutive days. The first dose and the dose at the Day 14 Visit will be administered in the study clinic by the participant mother, or by the IoR/designee as necessary.

6.2 Administration

Study participant mothers will be instructed to insert one dose (the entire contents of one applicator) of product into the vagina once each day for 28 days or until delivery,

whichever comes first, without regard to sexual activity. They will be instructed to insert their gel as close to the same time each day as possible.

If a daily dose is missed, the participant mother is instructed to administer the missed dose as soon as possible, unless the next dose is due within 6 hours. If the next dose is due within 6 hours, the missed dose will be skipped and the next dose will be administered as originally scheduled.

6.3 Study Product Formulation

6.3.1 1% Tenofovir Gel

Tenofovir 1% gel is a gel formulation of tenofovir (PMPA, 9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate), formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, HEC, and pH adjusted to 4-5. Tenofovir 1% gel is a transparent, viscous gel. Each dose administered will be approximately 4 mL of gel containing approximately 40 mg of tenofovir. Tenofovir 1% gel should be stored at 25°C (77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F).

6.3.2 Placebo for Tenofovir Gel

Universal HEC Placebo gel contains HEC as the gel thickener, purified water, sodium chloride, sorbic acid and sodium hydroxide. The gel is isotonic and formulated at a pH of 4.4 to avoid disrupting the normal vaginal pH and has minimal buffering capacity to avoid the inactivation of sexually transmitted pathogens. Hydroxyethylcellulose, the gelling agent, is used to approximate the viscosity of other microbicide gel candidates. Each pre-filled applicator will contain approximately 4 mL of Universal HEC Placebo gel for delivery.[51]

Universal HEC Placebo gel should be stored at 25°C (77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F).

6.4 Study Product Supply and Accountability

6.4.1 Study Product Supply

Universal HEC Placebo gel and 1% tenofovir gel will be supplied by CONRAD (Arlington, VA, USA).

6.4.2 Study Product Accountability

The MTN CRS Pharmacist of Record is required to maintain complete records of all study products received and subsequently dispensed. All unused study products must be returned to the CRPMC after the study is completed or terminated unless otherwise instructed by the DAIDS Protocol Pharmacist. The procedures to be followed are provided in the manual, *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials*

Networks. Non-US sites will follow the instructions provided in the manual for Study Product Destruction.

6.5 Study Product Dispensing

Study products will be dispensed by the pharmacist only for enrolled participant mothers, upon receipt of a written prescription signed by an authorized prescriber. Thirty pre-filled applicators of 1% tenofovir gel or Universal HEC Placebo gel will be dispensed on Day 0. This will provide participant mothers two extra applicators, should one or two of the prefilled applicators not be usable.

6.6 Retrieval of Unused Study Products

It is anticipated that two unused applicators will be returned to the study site on Day 28 unless replacement applicator(s) is/are needed by the participant mother during the 28 days of administration. Study participant mothers will be instructed to return all unused applicators to the site at the Day 28 visit. Unused applicators will be returned to the pharmacy where they will be counted and documented before being placed in quarantine.

It is important to note that for the majority of participant mothers in MTN-019, unused study product will be collected at their Day 28 Visit. However, for participant mothers who deliver prior to the end of their scheduled product use period, product will be collected at the Pregnancy Outcome Visit. Product may be collected at other times, in the following contexts:

1. If the participant mother desires to return the product earlier, e.g., at the Delivery Visit.
2. If the participant mother fails to bring the product to the Pregnancy Outcome Visit, study staff may arrange for the participant mother to return to the clinic with study product, or retrieve the product from the participant mother at another location.

6.7 Study Product Adherence Assessment and Counseling

Study product adherence assessment will include drug levels, self-reported adherence, and count of returned unused applicators. Study product adherence counseling will be provided at Enrollment, Day 7, and Day 14, and may be provided at Interim Visits, if indicated. Counseling will be based on the client-centered model developed for VOICE, and will focus on the participant mothers' experience using the product, and how to overcome barriers to use.

6.8 Concomitant Medications

Enrolled study participant mothers may use concomitant medications during study participation. All concomitant medications, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs, and herbal preparations reported throughout the course of the study, beginning at Enrollment, will be recorded on case report forms (CRFs) designated for that purpose. Should a participant mother report

use of a medication for which concomitant use poses significant risk to the participant mother, according to the clinical judgment of the IoR/designee, the IoR/designee will institute a temporary product hold, for as long as the participant mother is taking the medication. There are no known contraindicated medications for MTN-019, except for other antiretroviral drugs (e.g., didanosine, atazanavir, lopinavir/ritonavir) which are not relevant, since HIV infection is an exclusion to study participation. Study product will be discontinued for participant mothers who report taking PEP for HIV exposure. All participant mothers will be counseled to avoid the use of spermicides, traditional vaginal agents, and other non-study vaginal products (other than female condoms). Participant mothers who report use of these products will be counseled regarding the use of alternative methods, but reported use of these products does not require any change in use of study products. Condoms provided by study staff will not be coated with any type of spermicide.

6.9 Recommended Medications and Procedures

Study sites will be provided condoms to be distributed to study participant mothers for use during study participation, as sexual activity is not restricted by the trial. These condoms will contain an aqueous lubricant and will not be impregnated or coated with spermicide. Instructions and counseling on the use of these products will be provided as needed. In the event that a participant mother needs additional male condoms between visits, she may request these from clinic staff at any time.

Study sites will offer participant mothers a single brand of panty liners (unscented and breathable) to study participant mothers for use during study participation. Panty liners may be requested from clinic staff at any time including in between visits.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is presented in Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites are provided in the MTN-019 SSP Manual available at www.mtnstopshiv.org. Unless otherwise specified, the laboratory procedures listed in this section are performed at the local study site laboratories.

7.1 Pre-Screening

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

requirements. Participant mothers may be pre-screened for the subsequent group not yet open for enrollment, with attention to the participant mother's gestational age and the screening window.

7.2 Screening

A Screening Visit may take place up to 42 days prior to the Enrollment Visit (Day 0). Screening procedures may be completed over multiple visits, if necessary. Participant mothers will be instructed to bring antenatal records (e.g., antenatal care card) with them to the Screening Visit, if possible, to expedite the screening process. Participant mothers will also provide written permission for the study site to obtain copies of their records, including laboratory and ultrasound results, for review prior to final confirmation of eligibility for Enrollment.

7.2.1 Administrative, Behavioral, and Regulatory Procedures

- Informed consent for screening
- Co-enrollment assessment (site-specific)
- Assign participant identification number (PTID) to participant mother
- Demographic information
- Behavioral assessment (for eligibility)
- Locator information
- HIV pre- and post-test counseling (including risk reduction counseling)
- Offer HIV counseling and testing for partner(s)
- Obtain signed medical records release and antenatal provider information, planned location for delivery
- Reimbursement
- Schedule next visit (if applicable)

7.2.2 Clinical Procedures

- Medical history (including exclusionary medical conditions and medications during the current pregnancy)
- Obstetric (OB) symptom review (including genital bleeding, contractions, possible loss of amniotic fluid, normal fetal movement [if expected for gestational age])
- Review available antenatal records
- Review ultrasound results (conduct or refer for ultrasound, if ultrasound results are incomplete or unavailable, according to judgment of the IoR/designee)
- Calculation of gestational age using criteria in Section 7.14
- Full physical exam, including weight and vital signs
- Height
- Obstetric abdominal exam
    - Inspection
    - Palpation
    - Fundal height

- Auscultation of fetal heart tones (by Doppler, fetoscope or ultrasound), including rate (if appropriate for gestational age)
- Pelvic exam to include the following:
  - Visual inspection
  - Vaginal swab, if indicated to evaluate symptomatic vaginitis
  - Cervical sampling for Pap smear (if clinically indicated, at sites with capacity, where standard of care)
- Blood collection
- Urine collection
- Disclosure of available test results
- Treatment or referral of conditions identified at Screening, according to local standard of care (treatment of symptomatic BV is encouraged)
- Offer / refer for partner STI testing and treatment, if indicated

7.2.3 Laboratory Procedures

- Urine
  - HCG
  - NAAT for GC/CT
  - Urine dipstick for protein and glucose
- Blood
  - HIV serology
  - Complete blood count with platelets
  - Creatinine
  - AST/ALT
  - HBsAg
  - Syphilis testing
  - Malaria (at sites with capacity, where women are at risk and testing through antenatal care provider is not otherwise available, with results managed according to standard of care)
- Pelvic
  - Vaginitis testing, if symptomatic (KOH, wet prep, pH)
  - Trichomonas testing
  - Evaluation of Pap smear, at sites with capacity, where standard of care

7.2.4 Study Supplies

- Condoms

7.2.5 Final Screening Procedures and Confirmation of Eligibility

Before proceeding with the Enrollment or “on study” procedures described in Section 7.3, the following procedures will be performed on anticipated day of Enrollment to confirm participant mother eligibility:

- Review all screening laboratory results and other prior screening documentation

- Confirm calculation of gestational age using criteria in Section 7.14
- Update medical history and/or current medications, if applicable
- Re-confirmation of medical eligibility
- Re-confirmation of behavioral eligibility
- Blood collection and HIV serology, HIV pre- and post-test counseling
- Any other clinically indicated behavioral, clinical, or laboratory assessments

7.3 Enrollment (Day 0)

7.3.1 Administrative, Behavioral, and Regulatory Procedures

- Informed consent for enrollment
- Informed consent for storage of specimens and future testing
- Locator information
- Update signed medical records release and antenatal provider information, planned location for delivery, if indicated
- Baseline Behavioral Assessment
- Randomization
- Study product instructions and adherence counseling
- Reimbursement
- Schedule next visit

7.3.2 Clinical Procedures

- Update medical history
- Obstetric symptom review
- Update concomitant medications
- Vital signs
- Pelvic exam (external and internal inspection, bimanual exam)
    - Collection of vaginal swabs
    - Collection of cervical swabs
- Obstetric abdominal exam
    - Fundal height
    - Fetal heart tones (by Doppler, fetoscope or ultrasound)
- Blood collection
- First study gel application in study clinic (by participant mother or by IoR/designee, if necessary)
- Disclosure of available test results, if indicated
- Treatment or referral of conditions, if indicated
- Collect AEs (following gel insertion)
- Ultrasound, if indicated

7.3.3 Laboratory Procedures

- Vaginal swab for biomarkers

- Cervical swab for biomarkers
- Vaginal pH
- Vaginal culture at selected sites (approved by NL)
- Gram stained vaginal smear
- Vaginitis testing, if symptomatic (KOH, wet prep)
- Trichomonas testing, if clinically indicated
- Blood biomarkers
- Plasma archive

Note, plasma archive is collected on all participant mothers on the day of Enrollment, and may be collected during blood draw used for testing related to final confirmation of eligibility, provided informed consent has been documented for this specimen collection.

Note: blood biomarkers will be selected based on findings from relevant related trials, including MTN-003, MTN-008, and other emerging data.

7.3.4 Study Supplies

- Provision of condoms and panty liners
- Provision of study product,

7.4 Days 7 and 14 Visits

7.4.1 Administrative, Behavioral, and Regulatory Procedures

- Update locator information
- Update signed medical records release and antenatal provider information, planned location for delivery, if indicated
- Behavioral assessment
- Adherence assessment
- Adherence counseling
- Reimbursement
- Schedule next visit

7.4.2 Clinical Procedures

- Update medical history
- Review available antenatal records, if indicated
- Obstetric symptom review
- Update concomitant medications
- Vital signs
- Obstetric abdominal exam
  - Inspection
  - Palpation
  - Auscultation of fetal heart tones (by Doppler, fetoscope or ultrasound), including rate
- Physical exam, if indicated

- Pelvic exam, if clinically indicated (indications may include, but are not limited to genital symptoms, uterine contractions, or abnormal findings on other examinations)
- Collect/update AEs
- Social harms assessment
- Disclosure of available test results, if indicated
- Treatment or referral of conditions, if indicated
- Blood collection (Day 14)
- Urine collection, if indicated
- Ultrasound, if clinically indicated for evaluation of a primary study endpoint (e.g., suspected placenta previa)
- Insert gel in clinic (Day 14 only)

7.4.3 Laboratory Procedures

- Creatinine (Day 14)
- AST/ALT (Day 14)
- TFV level
- Vaginitis testing, if symptomatic (KOH, wet prep, pH)
- Trichomonas testing, if clinically indicated
- GC/CT testing, if clinically indicated

7.4.4 Study Supplies

- Provision of condoms and panty liners

7.5 Day 28 Visit

7.5.1 Administrative, Behavioral, and Regulatory Procedures

- Update locator information
- Update signed medical records release and antenatal provider information, planned location for delivery, if indicated
- Behavioral assessment
- Adherence assessment
- HIV pre- and post-test counseling
- Offer of HIV counseling and testing for partner(s)
- Reimbursement
- Schedule next visit if indicated

7.5.2 Clinical Procedures

- Update medical history
- Review available antenatal records
- Obstetric symptom review
- Update concomitant medications

- Full physical exam, including weight and vital signs
- Obstetric abdominal exam
  - Inspection
  - Palpation
  - Fundal height
  - Auscultation of fetal heart tones (by Doppler, fetoscope or ultrasound), including rate
- Pelvic exam (see Section 7.12)
  - Collection of vaginal swabs
  - Collection of cervical swabs
- Collect/update AEs
- Social harms assessment
- Disclosure of available test results
- Treatment or referral of conditions, according to local standard of care
- Blood collection
- Urine collection, if indicated
- Ultrasound, if clinically indicated for evaluation of a primary study endpoint

7.5.3 Laboratory Procedures

- Creatinine
- AST/ALT
- HIV serology
- TFV level
- HBsAg, if indicated
- Blood biomarkers
- Vaginal pH
- Gram stained vaginal smear
- Vaginal swab culture at selected sites (approved by MTN NL)
- Vaginal swab for biomarkers
- Cervical swab for biomarkers
- Vaginitis testing, if symptomatic (KOH, wet prep)
- Trichomonas testing, if clinically indicated
- GC/CT testing, if clinically indicated

7.5.4 Study Supplies

- Provision of condoms
- Collect unused study gel

7.6 Post-dosing Follow-up Visits Prior to Pregnancy Outcome

Participant mothers will have a follow-up visit two weeks (i.e., 14 days) following the end of study product dosing, and then every four weeks (i.e., 28 days) until pregnancy outcome. With approved SOP's, appropriate components of these visits (e.g., not to

include pelvic exam) may be completed off-site. These visits may not occur for all participant mothers, due to proximity of delivery (especially Group 1).

7.6.1 Administrative, Behavioral, and Regulatory Procedures

- Update locator information
- Update signed medical records release and antenatal provider information, planned location for delivery, if indicated
- HIV pre- and post-test counseling
- Offer of HIV counseling and testing for partner(s)
- Reimbursement
- Schedule next visit, if indicated

7.6.2 Clinical Procedures

- Antenatal records review
- Update medical history
- Obstetric symptom review
- Update concomitant medications
- Physical exam, including weight and vital signs, if indicated
- Obstetric abdominal exam
  - Inspection
  - Palpation
  - Fundal height
  - Auscultation of fetal heart tones (by Doppler, fetoscope or ultrasound),
- Pelvic exam, if indicated
- Collect/update AEs
- Social harms assessment
- Disclosure of available test results, if indicated
- Treatment or referral of conditions, according to local standard of care
- Blood collection
- Ultrasound, if indicated

7.6.3 Laboratory Procedures

- HIV serology
- Blood biomarkers (with consent)

7.6.4 Study Supplies

- Provision of condoms
- Collect unused product, if any remains to be collected from participant mother

7.7 Delivery Visit

A Delivery Visit will occur for participant mothers who have inserted study gel within 24 hours of arriving at the hospital for delivery. Study staff will travel to hospitals included in approved site SOPs. For the purpose of MTN-019 "onset of labor" is defined as admission to hospital for labor and delivery management, which would also include induction of labor and scheduled or unscheduled cesarean delivery. With IRB/EC approval, participant mothers may be reimbursed for notifying study staff regarding labor and/or travel to the hospital for delivery.

Procedures for this visit will include the following:

- Update locator information
- Update signed medical records release and antenatal provider information, if indicated
- Records review
- Update medical history
- Collect information on recent study gel use
- Concomitant medications
- Collect AEs
- Social harms assessment
- Reimbursement
- Collect blood from mother for drug level
- Collect blood from umbilical cord for drug level
- Collect delivery information
- Collect infant information
    - Length, weight, and head circumference of infant (may be performed by study staff if not available in medical records)
    - Estimated gestational age of infant

7.8 Pregnancy Outcome Visit

A Pregnancy Outcome Visit will be scheduled for the participant mother after the pregnancy outcome occurs. Study site staff will collect updated locator information, data regarding pregnancy outcome, adverse events, and any social harm for the mother and infant at this visit. Available clinical records for the mother and infant will be reviewed for updates to medical history, antenatal care, concomitant medications, and possible adverse events. Reimbursement will be provided. Study staff will update signed medical records release and antenatal provider information, and location for delivery, if indicated. This visit is conducted approximately 30 days after the date of the pregnancy outcome. Windows are specified in the MTN-019 SSP Manual (www.mtnstopshiv.org). Any study gel still remaining in the participant mother's possession should be collected at this visit. Home visits are allowable with an approved site SOP. If neither a site-based nor home visit can be completed, sites should endeavor to collect visit data via medical records and telephone. If indicated, additional follow-up visits may be scheduled.

7.9 Follow up Procedures for Participant Mothers Who Temporarily Hold or Permanently Discontinue Study Product

Clinical management guidance for participant mothers requiring product hold/discontinuation is included in Section 9.

Temporary Holds
All protocol-specified study procedures will continue except study product provision and product adherence counseling will be paused. Following a product adherence assessment to capture product use prior to the hold, adherence assessments will be paused.

Permanent Discontinuations
Further study product provision and counseling will discontinue. Following a final product adherence assessment, further adherence assessments will discontinue. Risk reduction counseling following diagnosis of HIV infection will be provided/modified according to local standards of care. Testing for HIV will discontinue following diagnosis of HIV infection. Participants who are diagnosed with HIV will be encouraged to continue follow-up in MTN-019.

7.10 Interim Visits

Interim visits will include clinically and otherwise indicated procedures, and may be performed at any time during the study, for the following or other reasons:

- For administrative reasons, e.g., a participant mother may have questions for study staff, or may need to re-schedule a follow-up visit.
- For product-related reasons, e.g., a participant mother may need additional study product or want to discuss problems with adherence to product use.
- In response to AEs. When interim contacts or visits are completed in response to participant mother reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care (see also Section 9).
- For interim STI counseling and testing in response to STI symptoms.
- For interim HIV counseling and testing in response to presumed exposure to HIV.
- To provide participant mothers with the results of confirmatory HIV test results
- For other reasons at participant mother request.

Given the specification of visit windows for this study, interim visits will occur when more than one visit takes place within an allowable visit window. All interim contacts and visits will be documented in participants' study records and on appropriate CRFs, when applicable. Locator information should be confirmed/updated at all interim visits.

7.11 Behavioral, Adherence and Acceptability Assessments

Using questionnaires we will assess product acceptability and the following behaviors:

- Study product adherence
- Sexual activity, including frequency of vaginal sex and condom use

- Intravaginal practices

A Baseline Behavioral and Acceptability Questionnaire will be administered in the clinic after initial insertion of gel has occurred at the Enrollment Visit. Participant mothers will be asked questions about sexual behavior, prevention method use and intravaginal practice history, and about their attitudes towards the physical properties of the gel, their attitudes and perceptions about using gel during pregnancy, and other preliminary acceptability measures of the gel. At the Day 7 and 14 Visits, participant mothers will report their use of gel, coital frequency, prevention method use and intravaginal practices on a Follow-up Adherence Questionnaire. At the Day 28 visit, they will be asked to complete the Follow-up Acceptability and Adherence Questionnaire which will include the same measures as Day 7 and 14, as well as acceptability questions similar to those from the Enrollment Visit and additional questions about their experiences using the gel, including reasons for non-use, if applicable, willingness to use in the future and beliefs around use of vaginal products during pregnancy, and any perceived effect on fetus/infant. The questionnaire will also assess attitudes and experiences using electronic monitoring, e.g., the Wisebag system, at sites with capacity. At sites with capacity, some questions may be asked via CASI and/or ACASI.

7.12 Clinical Evaluations and Procedures

Obstetric Abdominal Exams will include the following assessments:

- Appearance
- Palpation
- Fundal height (measured at baseline and 28-day Visit only)
- Auscultation of fetal heart tones (by Doppler, fetoscope or ultrasound), including rate (not measured following pregnancy outcome)

Physical exams will include the following assessments:

Vital signs

- Oral temperature
- Blood pressure
- Pulse
- Respirations

Clinical assessments

- Head/neck
- Lymph nodes
- Heart
- Lungs
- Extremities
- Weight

Pelvic exams will include external and internal (via speculum) inspection, as well as bimanual exam. Cervical exam will include dilation, effacement, consistency, position and fetal station (if applicable for gestational age, according to the clinical judgment of the IoR/designee).

7.13 Laboratory Evaluations

The location of laboratory evaluations will depend on laboratory capacity.

Local or Regional Laboratory

- Urine dipstick
- Complete blood count with platelets
- Creatinine
- AST/ALT
- HIV serology
- HBsAg
- Syphilis serology
- Vaginitis
- Trichomonas
- Chlamydia
- Gonorrhea
- Pap smear interpretation
- Malaria

Network Laboratories

- Blood TFV level
- Blood biomarkers

Pharmacokinetic Methods

The assay planned for MTN-019 has been approved by Clinical Pharmacology Quality Assurance which operates under contract with DAIDS. The validated liquid chromatography mass spectrometry method planned for MTN-019 has a LLOQ of 5 ng/mL.

7.14 Calculation of Gestational Age

Inconsistency or concern about the accuracy of the estimated gestational age requires further assessment with ultrasonography. Useful measurements include the crown–rump length of the fetus during the first trimester and the biparietal diameter or head circumference and femur length during the second trimester. Because of the normal variations in size of infants in the third trimester, dating the pregnancy at that time is less reliable (±21 days). The variation by ultrasonography generally is ±7 days up to 20 weeks of gestation, ±14 days between 20 and 30 weeks of gestation, and ±21 days beyond 30 weeks of gestation. If the estimated gestational age by the participant mother's last menstrual period differs from the ultrasound estimate by more than these accepted variations, the ultrasound estimate of gestational age should be used instead of the patient's menstrual cycle estimate.

7.15 Specimen Collection and Processing

Study sites will adhere to standards of good clinical laboratory practice, the HPTN-MTN Network Laboratory Manual (www.mtnstopshiv.org), DAIDS Laboratory Requirements (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/Laboratories.aspx), MTN-019 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.

7.16 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/Laboratories.aspx).

7.17 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by the 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. Participant mothers will be provided instructions on the safe disposal of used study gel applicators; applicators may be brought to the clinic site for disposal, if desired.

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(s), DAIDS, NICHD, and CONRAD Medical Officers, Protocol Safety Physician, and SCHARP Clinical Affairs Safety Associate will serve as the PSRT. The MTN SDMC prepares routine AE and clinical data reports (blinded to treatment assignment) for review by the PSRT, which meets via conference call approximately once per month or as needed throughout the period of study

implementation to review safety data, discuss product use management, and address any potential safety concerns. The content, format and frequency of the safety data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. The PSRT will also provide rapid consultation with site clinicians regarding management of toxicities as needed. Further guidance on safety monitoring during MTN-019 is included in Section 10.

The PSRT will conduct regular reviews of standardized study safety data reports. Per the MTN-019 Study Reporting Plan, the MTN Statistical and Data Management Center will distribute study safety data reports to MTN-019 PSRT members on a routine basis. The PSRT will review the reports via regularly-scheduled conference calls and discuss study safety issues and concerns. Safety concerns identified by the PSRT will be communicated by the protocol Medical Officers to the Division of AIDS and NICHD, and, if appropriate, to the MTN Investigators of Record at each study site. In addition, this information will be conveyed to the MTN Study Monitoring Committee as appropriate.

Study safety data reports prepared by the SDMC will be based on data received at SCHARP. For all enrolled participants, reportable AEs, product holds, and social harms will be collected on CRFs and faxed to SCHARP for entry into the study database. All AE CRFs received at SCHARP will be reviewed and coded by SDMC Clinical Affairs staff using the MedDRA coding dictionary. Unless otherwise decided by the PSRT, study safety data reports will include tables which list any Expedited Adverse Events (EAEs), SAEs, uncoded AEs by verbatim term and severity, AEs by body system/MedDRA preferred term, severity, and relationship to study product, and product holds/ discontinuations.

8.2 Adverse Events Definitions and Reporting Requirements

An AE is defined as any untoward medical occurrence in a clinical research participant, from the time of randomization through when she terminates from the study; it 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 from the time of randomization. The term “investigational product” for this study refers to both study products, as well as the study gel applicator.

Study participants are provided instructions for contacting the study site to report any untoward medical occurrences they may experience, except for possible life-threatening events, for which they are instructed to seek immediate emergency care. Where feasible and medically appropriate, participants are 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 are obtained and required data elements are recorded on study CRFs. All participants

reporting an untoward medical occurrence are followed clinically until the occurrence resolves (returns to baseline) or stabilizes.

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

- Mothers
  - All maternal genital, genitourinary, and reproductive system AEs
  - All pregnancy-related AEs
  - All AEs for mothers of severity Grade 2 or higher
  - All serious AEs for mothers, as defined by the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice
  - All AEs that result in permanent discontinuation of study product use
  - All laboratory test abnormalities for mothers that are not otherwise associated with a reported clinical AE
- Infants
  - All serious AEs for neonates (first 30 days of life) born from pregnancies followed during MTN-019 participation

For each study participant, AE documentation and reporting are undertaken throughout the scheduled duration of follow-up, i.e., through completion of the participant's Termination Visit.

The IoR/designee will grade the severity of each AE and, for AEs reported on CRFs, assess the relationship of the AE to study product. AE severity is graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification, August 2009), with the following exceptions:

- AEs not included in the Female Genital Grading Table or protocol-specific grading scales are graded by the DAIDS AE Grading Table Version 1.0, December 2004 (Clarification, August 2009). In cases where a genital AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies is the grading scale utilized.

  - Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs. All fetal losses will be reported by sites on CRFs to the Statistical and Data Management Center, and will be considered during safety reviews conducted by the Clinical Affairs Safety Associates at the SDMC, the DAIDS Medical Officer, Protocol Safety Review Team, and Study Monitoring Committee.
  - Genital bleeding clinically assessed to be expected is not an AE.
  - Asymptomatic BV will not be a reportable AE.

- Decreased fetal movement is not considered an AE. However, adverse events identified in the course of clinical evaluation of decreased fetal movement will be captured.
- Findings on electronic fetal monitoring strips are not considered AEs.

- Protocol-specific grading scales will be used for the following AEs:

  - Bleeding during pregnancy, prior to the onset of labor
    - Grade 0: None
    - Grade 1: Spotting or bleeding less than menses
    - Grade 2: Bleeding like menses or heavier, no intervention indicated
    - Grade 3: Profuse bleeding with dizziness or orthostatic hypertension, transfusion indicated
    - Grade 4: Potentially life-threatening profuse bleeding and/or shock

  - Hypertensive disorders of pregnancy
    - Grade 0: None
    - Grade 1: Pregnancy-induced hypertension
    - Grade 2: Mild preeclampsia
    - Grade 3: Severe preeclampsia
    - Grade 4: HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, eclampsia, or life-threatening sequelae of preeclampsia (e.g., pulmonary edema)

  - Gestational Diabetes
    - Grade 0: None
    - Grade 1: Diet-controlled, no or minimal interference with usual social and functional activities
    - Grade 2: Medication prescribed
    - Grade 3: Evidence of adverse effects on pregnancy secondary to diabetes
    - Grade 4: N/A

Generally speaking, MTN investigators are instructed to assign a single unifying diagnosis whenever possible. A term or description must be assigned to each AE, and whenever possible, a diagnosis is assigned. When not possible to assign a single diagnosis to describe a cluster of signs and/or symptoms, each sign and symptom must be documented as an individual AE.

The relationship of all AEs reported on CRFs is assessed based on the Manual for Expedited Reporting of Adverse Events to DAIDS, dated January 2010 (DAIDS EAE Manual), the product Package Inserts and/or Investigators Brochures (as applicable), and the clinical judgment of the IoR/designee. The DAIDS Table for Grading Adult and Pediatric Adverse Events, the Female Genital Grading Table for Use in Microbicide Studies, and the Manual for Expedited Reporting of Adverse Events to DAIDS are

available on the DAIDS Regulatory Support Center (RSC) web site: http://rsc.tech-res.com/safetyandpharmacovigilance/.

All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the exit visit, the status/outcome of the AE should be updated to "continuing at end of study participation" and the AE Log form should be re-faxed to SCHARP DataFax. For any SAEs/EAEs that are continuing at a participant's study exit visit, the IoR/designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the SAE/EAE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the study exit visit. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The MTN-019 PSRT may advise study staff as to whether follow-up may be modified or indicated further on a case by case basis. For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE Log CRFs based on the re-assessments.

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

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires hospitalization or prolongation of existing hospitalization
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a serious adverse drug experience when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above

Adverse Event Relationship to Study Product
The relationship of all AEs to study product will be assessed per the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, dated January 2010) and clinical judgment. The relationship categories that will be used for this study are:

- *Related*: There is a reasonable possibility that the AE may be related to the study agent(s)

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

8.3 Expedited Adverse Event Reporting Requirements

8.3.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

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

8.3.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agents for which expedited reporting are required are: 1% tenofovir gel, Universal Placebo gel and the study gel applicator.

8.3.3 Grading Severity of Events

The grading of severity of events and the reporting period will be the same as for all AEs, as described in Section 8.2. After the end of the Protocol-defined EAE Reporting Period stated above, sites must report serious, unexpected, clinical suspected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

8.3.4 Expedited AE Reporting Period

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

8.4 Regulatory Requirements

Information on all reported AEs will be included in reports to the U.S. FDA and other applicable government and regulatory authorities. Site IoRs/designees will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. Site IoRs/designees also will submit AE information and any other relevant safety information to their IRBs/ECs in accordance with IRB/EC requirements.

8.5 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 (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected are reported to responsible site IRBs/ECs at least annually, or 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-019 SSP Manual. While maintaining participant confidentiality, study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm, to minimize the potential occurrence of such harm.

9 CLINICAL MANAGEMENT

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

9.1 Grading System

AE severity grading is described in Section 8.2.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

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

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

- Acquisition of HIV-1 infection; such participant mothers will not resume product use at any time. Study product should be permanently discontinued beginning immediately upon recognition of the first reactive rapid HIV test. Note, the first scheduled HIV test during follow-up is at the end of scheduled study product use. Thus, HIV testing prior to the end of scheduled study product use would be performed for clinical indications. Given the length of scheduled study product use, as well as the time needed to confirm HIV infection with further laboratory testing, study product will be discontinued in this instance, rather than temporarily held.

- Acquisition of hepatitis B infection; such participant mothers will not resume product use at any time.

- Report of use of PEP for HIV exposure.

- Report of admission to hospital for delivery, including induction of delivery and cesarean delivery.

- Pregnancy loss.

A participant mother will be temporarily held from study product for any of the following reasons:

- Participant mother is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being (including risk due to social harm) by continuing product use, according to the judgment of the IoR/designee. The IoR/designee must consult the PSRT on all temporary product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation. If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time.

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

Grade 1 or 2

In general, a participant mother who develops a Grade 1 or 2 AE (including a complication of pregnancy) regardless of relatedness to study product that is not specifically addressed below may continue product use.

Grade 3

Participant mothers who develop a Grade 3 AE (including a complication of pregnancy) that is not specifically addressed below and is judged by the IoR/designee to be not related to study product may continue product use.

In general, and unless otherwise decided in consultation with the PSRT, if the event is deemed to be related to study product, the IoR/designee should:

- Temporarily hold the study product.
- Re-evaluate the participant mother at least weekly for up to 2 weeks.
- Resume study product if improvement to ≤ Grade 2 is documented within 2 weeks.
- Consult the PSRT if improvement to severity ≤ Grade 2 cannot be documented within 2 weeks.

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

Grade 4

A participant mother who develops a Grade 4 AE (including a complication of pregnancy) that is not specifically addressed below (regardless of relationship to study product) should have the study product held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT.

9.5 Management of Specific Toxicities

Specific temporary product hold requirements are specified here in the context of clinical management of toxicities.

9.5.1 Nausea, Vomiting, and Diarrhea

The IoR/designee may treat a participant mother with Grade 1 or 2 nausea, vomiting, and/or diarrhea symptomatically (e.g., diet changes, antiemetics, and/or supportive fluids). Unless other temporary product hold requirements apply, study product need not be held. If the IoR/designee chooses to hold product, the IoR/designee must consult the PSRT for further guidance on resuming product use, continuing the hold temporarily, or progressing to permanent discontinuation.

9.6 AST and/or ALT Elevations

Careful assessments should be done to rule out alcohol, non-study medication-related drug toxicity, herbal medications/supplements, HELLP syndrome, or viral hepatitis as the cause of elevation in AST and/or ALT of any grade. The IoR/designee must carefully assess the participant mother for any symptoms or signs of hepatoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, right upper quadrant pain or hepatomegaly. If hepatitis B infection is confirmed, product use must be permanently discontinued.

Unless other temporary product hold/permanent discontinuation requirements guidelines apply, study product need not be held unless the IoR/designee has compelling evidence that the toxicity is probably or definitely related to study product. In this case, the IoR/designee must consult the PSRT for further guidance on resuming product use, continuing the product hold temporarily, or progressing to permanent discontinuation.

9.7 Pap Smear

The IoR/designee should manage Pap smear results according to current guidelines of the American Society for Colposcopy and Cervical Pathology, unless other local guidelines are available. The IoR/designee must temporarily hold study product for participant mothers who require colposcopic evaluation of the cervix. The period of temporary product hold will begin on the day of the clinical evaluation, biopsy, and/or treatment of the abnormality. The period of temporary hold will continue after biopsy and/or treatment of the abnormality until a clinically acceptable resolution for the biopsy and/or treatment has occurred according to the judgment of the IoR/designee. Study staff will obtain medical records documenting the evaluation, biopsy, and/or treatment of the abnormality and, assuming adequate treatment is confirmed, will perform a pelvic exam after the evaluation/biopsy/treatment date to confirm healing of the cervix. Thereafter, assuming no contraindications are identified on pelvic exam, product use will be resumed.

9.8 Genital Sexually Transmitted Infection/Reproductive Tract Infection

The IoR/designee should manage STI/RTI per current CDC guidelines (http://www.cdc.gov), World Health Organization guidelines (http://www.who.int/en/), or other locally regulated guidelines, as applicable. 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.

9.9 HIV Infection

A participant mother who has a positive test for HIV must have study product permanently discontinued. Participant mothers identified as infected with HIV will be managed or referred for management according to the local standard of care.

At participating sites, MTN-019 participant mothers who become infected with HIV will be offered participation in MTN-015, the MTN Seroconverter Study, which also includes provisions for the clinical management and/or referral of participants infected with HIV. Participants will be referred for HIV-1 care and treatment, according to local guidelines; this referral process may also occur via MTN-015 if the participant chooses to enroll in that study. 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 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, such as those funded by the US President's Emergency Plan for AIDS Relief.

The level of care provided at the referral sites will meet or exceed the community standard for HIV-1 care. At every study visit, study staff will actively follow-up on prior referrals to HIV-1 care and support services, to determine whether the participant sought the care to which she was referred, the outcome of the referral, and whether additional referrals are needed. Additional counseling also may be needed to help ensure the participant receives appropriate care. All follow-up actions, outcomes, counseling, and plans for next steps will be documented in participant study records. Results of study laboratory testing may be helpful in clinical management; these results will be provided to the participant and her medical provider in real-time.

9.10 Hepatitis B Infection

If symptoms or signs of clinical hepatitis are present, the IoR/designee must test the participant mother for hepatitis (including HBsAg plus any other testing indicated by the local standard of care). Consideration should be given to other causes of hepatitis in pregnancy, including obstructive gall bladder or bile duct disease, severe preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy. If hepatitis is confirmed, product use must be permanently discontinued. Participant mothers identified as infected with hepatitis B will be managed or referred for management according to the local standard of care.

9.11 Signs/Symptoms of Labor

Temporary product hold should be instituted at onset of labor or rupture of membranes. If labor and rupture of membranes are ruled out, study product should be resumed. For the purposes of MTN-019, labor is defined as admission to care for labor and delivery management, which would also include induction of labor and cesarean delivery.

9.12 Criteria for Early Termination of Study Participation

Participant mothers may voluntarily withdraw from the study for any reason at any time. The IoR also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, including the Office for Human Research Protections (OHRP),

or site IRBs/ECs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume product use (if applicable) and follow-up through their originally scheduled study exit date, pending consultation with the PSRT for evaluation of eligibility.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is an expanded Phase 2, multi-site, double-blinded, two-arm, 2:1 randomized, placebo-controlled trial to assess and compare the safety of 1% TFV gel, when used continuously for 28 days (or until pregnancy outcome) by healthy, sexually active, HIV-uninfected, pregnant women, as compared with the Universal HEC Placebo gel. Approximately 114 women (in Group 1) and 90 women (in each of Groups 2, 3, and 4) (2/3 in the 1% tenofovir gel arm and 1/3 in the placebo arm) will be randomized in 4 different cohorts defined by gestational age for a total of 384 participant mothers, plus their newborn infants.

10.2 Study Endpoints

The study endpoints will be collected both in the woman and her infant. For the mother, the endpoints are pregnancy outcomes, serious adverse events, maternal grade 2 or higher adverse events, including specific lab abnormalities, specific genital/pelvic signs/symptoms, pregnancy complications, other grade 3 or higher AEs that are judged to be related to the study gel or applicator. For the infant, the endpoints include all neonatal serious adverse events (in the first 30 days of life).

10.3 Primary Study Hypotheses

The primary study hypothesis is that TFV gel does not pose additional risk to the mother or the infant.

10.4 Sample Size and Power Calculations

The study is designed to have 90 women use gel for 4 weeks in each of the gestational age cohorts. Based on emerging participant replacement needs within MTN-008, we recognize that approximately 20% of the women in Group 1 will deliver before they have completed 4 weeks of gel usage. Therefore, we plan to enroll 114 women into Group 1 to ensure that we have close to 90 women with 4 weeks of gel usage. If 90 women complete 4 weeks before enrollment into Group 1 is complete, we will stop enrollment into that arm. Although we plan to include all women in the final analyses, our power calculations assume 90 women in each cohort. We expect this to be conservative for the case where more than 90 women will be followed in Group 1.

Safety endpoints

The following power calculations assume that safety endpoints will be analyzed by cohort and not with the 4 cohorts grouped together. The proposed sample size in each cohort is approximately n = 90 women randomized into 2 arms in a 2:1 ratio giving 60 women in the 1% TFV gel arm and 30 women in the placebo arm.

As a means to characterize the statistical properties of this study Table 3 presents the probability of observing zero, at least one, and two or more safety endpoints among the 60 women in the 1% tenofovir gel arm in a single cohort for various 'true" event rates:

Table 7: Analysis of Safety Event Frequency

Event Rate	P (0 events | n = 60)	P (≥1 event | n = 60)	P (≥2 events | n = 60)
0.5%	74.0	26.0	3.7
1.0%	54.7	45.2	12.1
3.5%	11.8	88.2	62.5
5%	4.6	95.3	80.8
10%	0.18	99.8	98.6
15%	0	99.9	99.9

Additionally, the proposed sample size ensures that in a given cohort, if the true rate of toxicity in the 1% tenofovir arm is 5%, we have 80% power to exclude toxicity endpoints greater than 15%.

An additional aim of the study is to compare the safety between the two arms (1% TFV gel arm vs. Universal HEC Placebo arm). Assuming a two-sided Fisher's Exact test with $\alpha = 0.10$ and 90% power, Table 8 provides the difference in the rates of safety events (proportion of women experiencing the safety event of interest) between the 1% tenofovir arm and the placebo arm that is detectable with 90% power for a given rate in the placebo arm. For example, if the true rate of a given toxicity endpoint in the placebo arm is 3.3% (1 of 30 women experiencing a safety event), the proposed sample size provides 90% power to detect safety endpoint rates greater than 25.5% (21.7% with 80% power). It is acknowledged that power calculations do not account for length of follow-up, which will vary among participants.

Table 8: Difference in the Rates of Safety Events

Rate in Placebo Arm	Rate in a Drug Arm Detectable with 90% Power
3.3%	25.5
6.7%	32.5
16.7%	47.5
33.3%	67.5
50.0%	81.5

10.5 Participant Accrual, Follow-up and Retention

Each study site is expected to enroll approximately 4 - 12 participants per month. Participant accrual is anticipated to take approximately 24 months. Sites will make every effort to follow women through completion of the Pregnancy Outcome Visit. The target for retention will be 95% of enrolled participants over the study period.

10.6 Randomization

Participants will be randomized in a 2:1 ratio to the two arms of the study. Study arm randomization will be balanced within each site using blocking and across sites using stratification. Randomization scheme will be generated and maintained by the MTN SDMC. The MTN SDMC will provide each study site with one set of randomization envelopes to be stored and used in the study clinic. Clinic staff will assign these envelopes in sequential order, by envelope number, to eligible participants. Assignment of the randomization envelope is considered the effective act of participant enrollment/randomization. Clinic staff will prepare a written prescription contained within the envelope that, among other things, documents the randomization envelope number and randomization code indicating the product (1% TFV or placebo gel) and the Day 14 PK time point to which the participant was assigned. Multiple codes will be utilized to conceal and protect the randomization assignments in this study. Clinic staff will store assigned randomization envelopes and their contents in participants' study charts.

10.7 Blinding

Study staff and participants will be blinded to the random assignments of all study participants. All study gels will be supplied in identical, single-used applicators packaged in individual wrappers. Blinding will be maintained until all data are entered into the study database, all study endpoint data and other data included in the final analysis have been cleaned and verified, and the data are ready for final analysis. This will be explained to participants as part of the study.

There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. As described in Section 9, in the event that an investigator is concerned that a participant might be put at an undue risk by continuing product use, the IoR/designee may discontinue study product use by this participant; however, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator will notify the PSRT to consider and rule upon the request.

The PSRT and SMC may be provided with unblinded product coding information with closed study reports upon request. It is anticipated that the PSRT will remain blinded until the data are locked for each gestational age cohort, and would only review unblinded data for that cohort if there were concerns based on the summary data typically reviewed by the PSRT. If there are no concerns from the summary data, the next gestational cohort would be opened without an unblinded data review.

10.8 Data and Safety Monitoring and Analysis

10.8.1 MTN-019 PSRT Review of Safety Data

Ongoing Review
The MTN-019 PSRT will be convened immediately (optimally within 48 hours of PSRT awareness) to consider pausing both enrollment into the study and continued study product use among participants currently in follow-up under the following circumstances:

- If any mother or infant experience a life-threatening toxicity which is judged to be related to study drug
- If two or more women experience the same Grade 3 or higher adverse event that is judged to be related to study drug exposure
- If two or more infants experience SAEs judged to be related to in utero exposure to study product

Additionally, the PSRT and other members of the protocol team will continually conduct careful reviews of all relevant safety data and determine whether further accrual and product administration should be paused or permanently discontinued at any time during the trial. Such a decision may be made at any time that unacceptable type and/or frequency of adverse events have been observed.

Review to Permit Accrual in Subsequent Groups
Before proceeding to the next earlier gestational age Group, an interim review of all safety data for the current Group will occur. This review will occur when data are available for the Day 14 Visit after the last dose of study product use for the last woman in the Group. At this point, we expect that over 90% of women will have completed at least six weeks of follow-up after the end of their 28-day dosing period. All data regarding adverse events will be reviewed. Sites will not enroll into the subsequent group until notified by the study operations center that they may commence enrollment. Pre-screening for the subsequent group prior to this time is permissible.

The study team recognizes that it is not possible to pre-specify all potential scenarios that are clinically relevant for interim and final analysis, particularly in the context of anticipated emerging data from other trials of tenofovir use in pregnancy. However, as general guidance, the PSRT will review safety data collected in Pregnancy Group 1 to look for a significantly higher rate (e.g., approximately three times higher for events with a baseline rate of 5%) of pregnancy complications compared to controls. If this were noted at interim review, serious consideration would be given as to the prudence of enrolling and exposing women at preterm gestational ages to this product. A similar review will be performed for each subsequent Group prior to initiating accrual into the next Group.

10.8.2 Study Monitoring Committee

In addition to the safety monitoring done by the PSRT, the MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, adherence, and completion of primary and secondary endpoint assessments. These reviews will take place approximately every 4-6 months, or as needed or required by the SMC. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The SMC may consider recommending termination of this study if recruitment is lower than targeted, or if study data quality is poor. Although the predominant consideration would be pregnancy outcomes, if there are some repetitive significant high grade genital or lab toxicities that are related to the product, those data would become part of the consideration.

10.8.3 Data Analysis

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Within-treatment group assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). When use of formal testing to assess differences between users of the Universal HEC Placebo gel arm and users of 1% TFV gel is required, the following methods will be used: for binomial response variables: chi-square tests and logistic regression (or exact testing methods); for continuous variables: t-tests and linear regression.

To assess the adequacy of the randomization, participants in each of the two arms will be compared for baseline characteristics including demographics and laboratory measurements using descriptive statistics.

<u>Primary Safety Endpoints</u>

All women and their infants randomized into the study will be included in the primary analysis to be consistent with the Intent-to treat principle. To assess safety, the number and the percentages of participants experiencing each safety endpoint (see Protocol Summary) will be tabulated by study arm. Each participant will contribute once in each category (i.e., only for highest severity AE for each participant) for the calculation of event rates. Exact binomial confidence intervals will be calculated for each safety endpoint for each arm and Fisher's Exact test used to test for differences in event rates between the two arms. Reports to the SMC and PSRT, as well as the final study report, will tabulate reported AEs overall and by grade.

Secondary Pharmacokinetic Endpoints

All women will contribute samples to the PK endpoints. At the Day 14 visit, all women will report the time of their prior dose. Each woman will have blood collected for analysis of plasma tenofovir pre-dose, followed by an observed vaginal TFV gel dose, which is followed by a second blood collection. The timing of this second blood collection will be determined by randomization to one of 3 sample time windows: 1-3 hours, 3-5 hours, or 5-7 hours. In the randomization process, these will be weighted 2:1:1 to increase the number of subjects contributing to the 1-3 hour window. Since 2 hours was the most frequent T_{max} (time associated with C_{max}) noted in MTN-001[42-43], our intent is to enrich the sample to provide a more robust estimate of C_{max}.

All subjects' pre-and post-dose tenofovir blood plasma data will be used for the sparse sampling analysis, including the data provided from MTN-001. Using population PK modeling methods, these data will be iteratively fit to appropriate compartmental models with additional patient characteristics (weight, height, creatinine clearance, pregnancy, and gestational group). Once the basic population PK model is established, clinical covariates of interest (pregnancy status, gestational group) will be added to the model to test influence of these covariates on PK parameters of importance (volume of distribution and clearance). Testing pregnancy status will require pooling data from MTN-019 with data from MTN-001 subjects from selected comparable sites participating in MTN-001. More traditional PK assessments will be made by comparison of each sampling time assignment (pre-dose, 1-3, 3-5, 5-7 hours) and between gestational groups and to the external MTN-001 cohort. The MTN-001 cohort has a discrete time cohort (pre-dose, 2, 4, 6 hr) that can be combined, based on timing interval midpoint, with the sparsely sampled cohort (1-3, 3-5, 5-7 hours). PK parameter estimates from both methods will include T_{max}, C_{max}, and C_{tau}.

Secondary Adherence Endpoints

An important secondary analysis will focus on adherence to study gel. Self-reported adherence to product use will be measured according to the procedures schedule in Section 7, using self-report, drug levels and count of returned unused applicators. This data structure will permit (1) estimation of adherence rates; and (2) the testing of differences in adherence between the active product and the placebo.

Descriptive statistics will be used to estimate (1) at selected time points. Since the analysis will involve repeated observations, generalized estimating equations (GEE) methods and robust variance estimates, will be used to evaluate statistical significance and compute confidence intervals for (2).

10.8.4 Missing Data

If the probability of missing outcome data depends on covariates, then the methods described above may give biased inferences and point estimates. If a substantial amount of safety data is missing (a follow-up visit missing in at least 10% of participants), then secondary analyses of the endpoints will be conducted using methods that relax the missing completely at random assumption to a missing at

random assumption. For a univariate binary and quantitative outcome, respectively, a generalized linear model with a binomial or normal error distribution will be used for estimation and testing.

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. In general, non-ACASI data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocpolicy.pdf).

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, for each of the three investigational products tested, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval for the study product 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 FDA is notified.

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

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdf).

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by PPD (Wilmington, NC) in accordance with Requirements for On-Site Monitoring of DAIDS Funded and/or Sponsored Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/onsitemonitor_reqs.pdf). 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 investigational study products
- Assess implementation and documentation of internal site quality management procedures

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

13 HUMAN SUBJECTS PROTECTIONS

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

13.1 Institutional Review Boards/Ethics Committees

Section 13.7.1 provides information that may assist IRBs/ECs in classifying this protocol under the guidelines in the US Code of Federal Regulations.

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

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

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their 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

The US NIH Division of AIDS holds the IND application for this study. Copies of all regulatory documents submitted to this IND by DAIDS are forwarded by DAIDS to CONRAD, for cross-referencing with other INDs for the study products. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement executed by DAIDS and CONRAD.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chairs and DAIDS Medical Officer. Study implementation will also be guided by a common study-specific procedures manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN CORE, SDMC, NL and other designated members of the protocol team.

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

13.4 Risk Benefit Statement

13.4.1 Risks

General

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, greater than expected bleeding and/or bruising, swelling and/or infection. Pelvic examination may cause mild discomfort and/or vaginal bleeding or spotting. Disclosure of HIV and STI status may cause worry, sadness or depression. Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions.

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 or perceived as HIV-infected or at "high risk" for HIV infection, or because partners or family members object to study participation during pregnancy, etc.). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Participants in 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 products. In addition, participants could misunderstand the current experimental status of the study products (i.e., their unknown safety and unproven efficacy) and as a result increase their HIV risk behaviors while in the study.

1% Tenofovir Gel

Administration of tenofovir gel intravaginally has been associated with the following potential risks[35]:

- Abdominal pain
- Dryness, itching, burning, irritation or pain in the genital area
- Participants with hepatitis B infection might be at risk for development of tenofovir resistant hepatitis B. However, participants with known hepatitis B infection will not be eligible for enrollment.
- Drug resistance. It is not known what effect tenofovir gel could have on the HIV virus or HIV disease progression in HIV-infected participants or their partners. There is a theoretical risk that tenofovir absorbed systemically from vaginal tenofovir gel could result in mutations of the HIV virus in participants who become infected with HIV during the study, or their partner, if the partner is infected with HIV. Limited resistance data from HPTN 050 show no new resistance mutations in plasma or cervicovaginal lavage specimens after 14 days of tenofovir gel use. No participant had high level tenofovir mutations (e.g., K65R).[52] In CAPRISA 004, no tenofovir-related drug resistance was found in the women who acquired HIV infection during study follow-up.[1]
- Genital irritation in male partners, including mild pain (burning, irritation, discomfort) and pruritus[44]
- Mild, self-limiting diarrhea[1]

In the MTN-002 study, 16 pregnant women received TFV gel. TFV vaginal gel was very well-tolerated by the participants, with no vulvovaginal complaints related to the study product.[46] A total of 146 AEs were recorded: 112 among mothers and 34 among newborns. Ninety-four (84%) of the maternal AEs were mild or moderate and 18 (16%) were severe. None of the AEs were assessed as related to study product. Nearly all maternal AEs were related to the pregnancy, surgery and/or post-operative recovery. Among infants AEs, 33 (97%) were mild, one was moderate, and none were related to study product.

The MTN-008 study Pregnancy Cohort has not identified any serious safety concerns to date.

13.4.2 Benefits

Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may contribute to the development of safe and effective interventions to prevent HIV transmission among pregnant women. Participants also may appreciate the opportunity to contribute to the field of HIV prevention research.

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical examination, pelvic examination, and routine laboratory testing related to blood, liver, and kidney function. Participants will be provided STI treatment in accordance with

local guidelines free of charge, and offered STI testing and treatment for their partners. Hepatitis B vaccine may be available to participants, depending on local guidelines for Hepatitis B vaccination in pregnancy. 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.

The CAPRISA 004 study recently demonstrated a 39% reduction in HIV acquisition, incidence rate ratio (IRR) = 0.61, 95% CI: 0.4-0.94, among participants who used tenofovir 1% gel in a pericoital regimen.[1] This trial also found a 51% protective effect against HSV-2 acquisition among women randomized to a coitally dependent regimen of tenofovir gel.[1] However, these findings have not yet been confirmed in another trial using either a pericoital or daily regimen, or among a population of pregnant women. Thus, the intervention under investigation in this trial (which is enrolling only women who report recent sexual activity) holds out the prospect of direct benefit for pregnant women.

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to both screening and enrollment. Written informed consent also will be obtained for long-term specimen storage and possible future testing, although consent for specimen storage is not required for study participation. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocpolicy.pdf). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

Each study site is responsible for developing study informed consent forms for local use, based on the templates in the Appendices that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

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

The informed consent process will cover all elements of informed consent required by research regulations, and will include an assessment of each potential participant's understanding prior to enrollment and randomization of concepts identified by the protocol team as essential to the informed consent decision. Participants who are not able to demonstrate adequate understanding of key concepts will not be enrolled in the study.

The MTN has obtained a Certificate of Confidentiality from the US Department of Health and Human Services that will be applicable for this study at US sites only. 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.

13.6 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. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- US NIH and/or its contractors, including study monitors
- The US FDA and/or other government and regulatory authorities
- The Office for Human Research Protections
- Representatives of CONRAD
- Representatives of the MTN CORE, SDMC, and/or NL
- Site IRBs/ECs

13.7 Special Populations

13.7.1 Pregnant Women

Based on an assessment of potential risks and benefits associated with the MTN-019 study products and procedures, the MTN-019 protocol team provides the following rationale to support the assertion that this protocol may be conducted, as specified in the US CFR, Subchapter A – Protection of Human Subjects, Subpart B, 46.204 – Research involving pregnant women or fetuses. Final determination rests with each site's local IRB/EC.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

a. ***Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.*** To date, preclinical studies, including pregnant animals, and clinical studies, including studies on non-pregnant women, have not identified significant safety risks to pregnant women and fetuses. Reassuring safety data from HPTN 059, CAPRISA 004, MTN-001 and MTN-002 are especially pertinent here. Further information is included in Section 2 of this protocol.

b. ***The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.*** Due to projected low exposure to tenofovir for the fetus (based on PK data from MTN-001 in non-pregnant women and MTN-002 in pregnant women), associated risks are expected to be minimal. In addition, recent evidence pointing to the protective effect of tenofovir gel against HIV and HSV-2 in women holds out the prospect of direct benefit to both the woman (reasonably presumed to have been sexually active in the recent past, due to both self-report and pregnant state) and the fetus, as primary maternal infection with HIV or HSV poses significant risk to the fetus. Further information on the evidence surrounding the potential protective benefits of tenofovir gel is also included in Section 2.

c. ***Any risk is the least possible for achieving the objectives of the research.*** The protocol has minimized risk by taking a carefully monitored, step-wise approach to dosing, starting at later gestational ages, then progressing earlier in pregnancy once safety is confirmed.

d. ***If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part.*** The protocol includes an informed consent process consistent with all applicable requirements in the CFR.

e. ***If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part,***

except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest. This section is not applicable, as there is the prospect of direct benefit to the pregnant woman.

f. ***Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.*** This information has been included in the Sample Informed Consent documents, will be included in site-specific informed consent documents, and will be covered thoroughly during the informed consent process, including throughout the pregnant woman's participation in the study. In addition, the pregnant woman will be informed of any applicable new information learned throughout this or other studies.

g. ***For children as defined in 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part.*** This section is not applicable to MTN-019, as children under 18 years old who are pregnant will not be enrolled.

h. ***No inducements, monetary or otherwise, will be offered to terminate a pregnancy.*** Inducements to terminate a pregnancy will not be offered by study site staff.

i. ***Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.*** Individuals engaged in MTN-019 will have no part in decisions as to the timing, method, or procedures used to terminate a pregnancy by participants.

j. ***Individuals engaged in the research will have no part in determining the viability of a neonate.*** Individuals engaged in MTN-019 will have no part in determining the viability of a neonate.

13.7.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study will enroll newborns of participant mothers.

13.8 Compensation

Pending IRB/EC approval, participants will be compensated for time, effort, and other IRB/EC-approved expenses (e.g., transportation to designated hospital).

13.9 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV 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 participant mothers who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled participant mothers at each follow-up HIV testing time point. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site. In accordance with the policies of the NIH, participant mothers must receive their HIV test results to take part in this study. Condoms will be provided to participant mothers throughout the duration of their participation. Post-test counseling should include risk reduction counseling, as appropriate.

13.10.2 Care for Participants Identified as HIV-Infected

Care for participants identified as HIV-infected is described in Section 9.9. Participants identified as HIV-infected will be referred to available resources for PMTCT.

13.11 Study Discontinuation

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

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies and a Clinical Trial Agreement between CONRAD and NIAID will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS, NICHD, NIMH, and CONRAD for review prior to submission. Results of the trial will be shared per sponsor dissemination policies and according to guidance from MTN, within embargo and after embargo.

15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

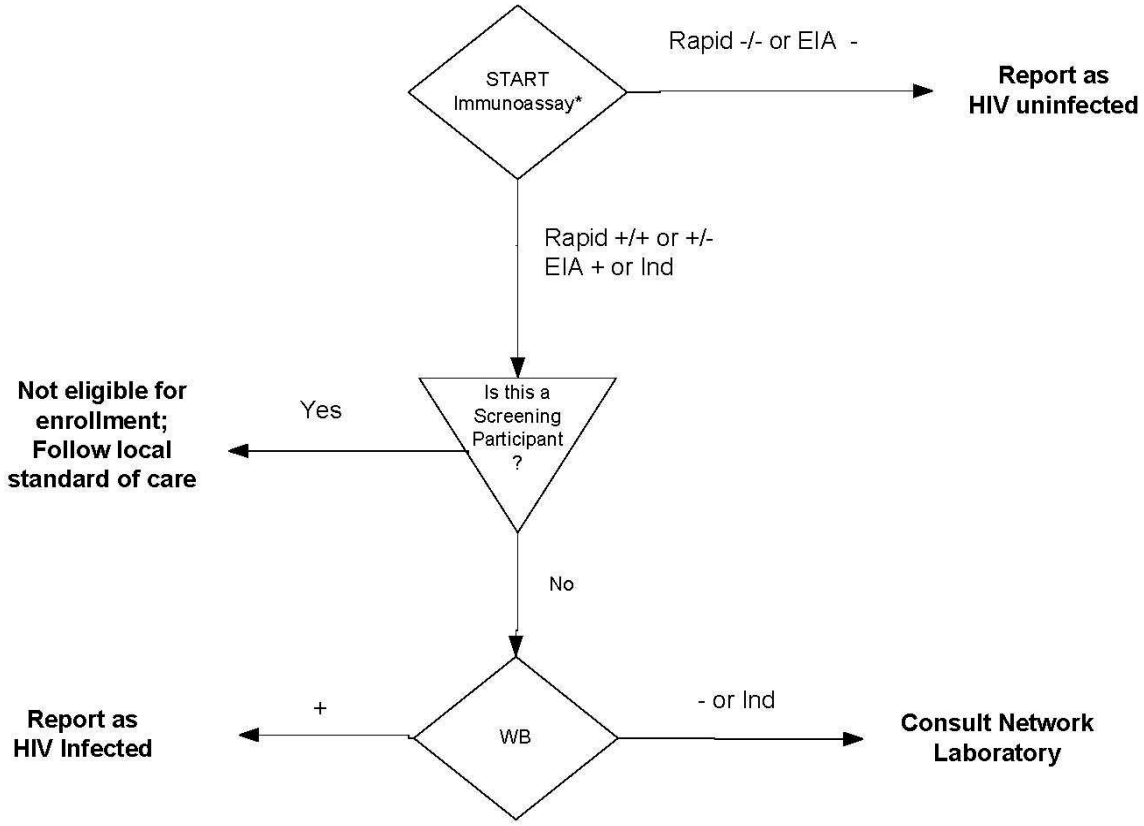
			SCR	ENR	DAY 7	DAY 14	DAY 28	POST	INT	OUTCOME
ADMINISTRATIVE, BEHAVIORAL, REGULATORY	Informed consent(s)		X	X						
	Assignment of PTID		X							
	Locator information		X	X	X	X	X	X	X	X
	Records release/provider info./delivery location		X	*	*	*	*	*	*	*
	Co-enrollment assessment		X							
	Demographic information		X							
	Eligibility assessment		X							
	Eligibility confirmation									
	Randomization			X						
	Reimbursement		X	X	X	X	X	X	*	X
	Schedule next visit		*	X	X	X	X	*	*	*
	Behavioral assessment		X	X	X	X	X		*	
	Adherence assessment				X	X	X		*	
	Adherence counseling			X	X	X			*	
	HIV pre/post counseling		X				X	X	*	
	Offer HIV counseling/testing partner		X				X	X	*	
CLINICAL	Concomitant medications		X	X	X	X	X	X	*	X
	Antenatal records		X		*	*	X	X	*	X
	Medical history		X	X	X	X	X	X	*	X
	OB symptom review		X	X	X	X	X	X	*	
	Calculate gestational age		X						*	
	Blood collection		X	X		X	X	X	*	
	Blood collection (post-dose PK)					X				
	Urine collection		X		*	*	*		*	
	OB abdominal exam		X	X	X	X	X	X	*	
	Phys. exam, weight		X		*	*	X	*	*	
	Height		X						*	
	Vital signs		X	X	X	X	X	*	*	
	Pelvic exam		X	X	*	*	X	*	*	
	Pelvic swab collection		X	X			X		*	
	Conduct/Refer for ultrasound		X	*	*	*	*	*	*	
	Treatment/Referral		X	*	*	*	*	*	*	
	Partner STI treatment/referral		*						*	
	In-clinic gel insertion			X		X				
	Test results		X	*	*	*	*	*	*	
	Collect/Update AEs and social harms			X	X	X	X	X	*	X
	Pregnancy outcome data									X
	Infant/delivery data									X
LABORATORY	Urine	Dipstick UA	X							
		HCG	X							
		GC/CT	X		*	*	*			
	Blood	HIV-1	X				X	X	*	
		Creatinine/AST/ALT	X			X	X		*	
		CBC with platelets	X						*	
		Tenofovir				X	X		*	
		Syphilis	X						*	
		HBsAg	X				*		*	
		Blood biomarkers		X			X	C		
		Malaria	*						*	
		Plasma archive		X						
	Pelvic	Pap smear	*						*	
		Vaginitis	*	*	*	*	*		*	
		Trichomonas	X	*	*	*	*		*	
		Biomarker swabs		X			X			
		Vaginal Culture		ANL			ANL		*	
		Gram stain		X			X		*	
		pH	*	X			X		*	
SUPP.	Provide condoms		X	X	X	X	X	X	*	
	Provide panty liners			X	X	X			*	
	Provide study product			X					*	
	Collect unused product						X	*	*	

*=as indicated, ANL=approved by NL. C=provided consent for blood biomarker testing during post-dosing period. POST=Post-Dosing Follow-Up Visit prior to Pregnancy Outcome. INT=Interim. OUTCOME=Pregnancy Outcome Visit. **Section 7.2.5 describes final confirmation of eligibility as part of screening procedures performed on expected day of Enrollment.**

DELIVERY VISIT	
ADMINISTRATIVE/BEHAVIORAL/REGULATORY	
Locator information	X
Update signed medical records release and antenatal provider information	*
Reimbursement	X
Schedule next visit	X
Adherence assessment	X
CLINICAL	
Concomitant medications	X
Medical history	X
Blood collection	X
Blood collection (cord)	X
Collect/Update AEs and social harms	X
Pregnancy outcome data	X
Infant/delivery data	X
LABORATORY	
Tenofovir level	X
STUDY SUPPLIES	
Collect unused product	*

***if indicated**

APPENDIX II: ALGORITHM FOR HIV TESTING – SCREENING AND ENROLLMENT



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

APPENDIX III: SAMPLE INFORMED CONSENT FORM (SCREENING)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-019

Phase 2 Expanded Safety Study of Tenofovir Gel in Pregnancy

[DATE]

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study:

INFORMED CONSENT
You are being asked to volunteer for screening tests to find out if you are eligible for a research study known as MTN-019. MTN-019 is for healthy, sexually active women who are pregnant with one baby, and planning on delivering in a hospital. MTN-019's purpose is to collect more information about the safety of tenofovir gel during pregnancy. Screening includes questions, blood tests, and physical and genital exams. The US National Institutes of Heath is funding the study. About 384 women and their newborns will join MTN-019 at clinics in the US and Africa. We will explain the purpose of screening, risks and benefits to you, and what is expected of you. Please ask questions about anything you do not understand or want to learn more about.

YOUR PARTICIPATION IS VOLUNTARY
This consent form gives information about screening in MTN-019. Once you understand the form, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep. You do not have to have the screening tests if you do not want to. You may decide not to have the screening tests, or to withdraw at any time after signing this form, without losing your regular medical care. Even if you agree to do the screening tests, you do not have to join MTN-019. If you decide not to have the screening tests, you can join another study later, if one is available and you qualify. If you join MTN-019, you should not join other studies of drugs, vaccines, medical devices or vaginal products for the time you are in MTN-019. There may be other places where you can access the same tests or other research studies going on; we will tell you about these places if you are interested. You should not use spermicides or other vaginal products while you are in MTN-019 (female condoms are allowed).

PURPOSE OF THE SCREENING TESTS AND THE STUDY
The purpose of the screening tests is to find out if you are eligible for MTN-019. Some people may not be able to join MTN-019 because of results of screening tests. You will receive test results even if you are not eligible to join MTN-019.

The main purpose of MTN-019 is test the safety of tenofovir gel when used daily for up to 28 days during four different times in pregnancy. You can only participate in one of the following groups:

- Group 1: 36 0/7 weeks – 37 6/7 weeks (about 114 women)
- Group 2: 28 0/7 weeks – 32 6/7 weeks (about 90 women)
- Group 3: 20 0/7 weeks – 24 6/7 weeks (about 90 women)
- Group 4: 12 0/7 weeks – 16 6/7 weeks (about 90 women)

You are being screened for: *[site to insert Group #].* Some of the screening tests will be used to confirm your pregnancy is the right age for this group.

PROCEDURES

For you to join MTN-019, all screening tests must be completed within 6 weeks after you sign this form. If all tests are not done within 6 weeks, and you want to join MTN-019, you will have to do all screening tests again. Screening will begin after you discuss, understand and sign or mark this form. We will answer your questions before you sign or mark this form. Procedures at this visit take about [*insert time*].

- We will ask where you live and other questions about you, your sexual activity, your health and pregnancy, your antenatal care provider, and where you plan to deliver.
- You will give urine for a pregnancy test and to test the health of your kidneys.
- You will talk with staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex. You will give blood (XX mL) for HIV testing. You will be told your result as soon as it is available (results take [*insert estimate*]). You will talk with us about your results and how you feel about them. Sometimes HIV tests are not clearly positive or negative. In that case, we do more tests until we know your status for sure. You must receive your HIV test results to join MTN-019. If you have HIV, you are ineligible for MTN-019. We will refer you to sources of medical care and other available services.
- Study staff will also test your blood for:
    - The health of your liver, kidneys and blood.
    - Hepatitis B. This is a liver infection that can pass from mother to baby, through sex or through body fluids infected with hepatitis B. If tests show you have hepatitis B active in your liver, you are not eligible for MTN-019.
    - Syphilis, an infection passed by sex
    - Malaria, if you live in an area where malaria is common
- You will have a physical exam, height and weight checks, measurement of your abdomen, and check of the baby's heartbeat (depending on age of your pregnancy)
- You will have an exam of your genital area and inside your vagina, including your cervix. The cervix is the lower part of the womb. Study staff may collect fluid from your vagina with swabs to test for trichomonas infection, and other vaginal infections if necessary. *[if applicable at site: You will have a Pap smear if one is due for you.]*
- You will have or be referred for an ultrasound of your pregnancy. The ultrasound uses sound waves to make a picture (on a computer screen) of a baby in the womb.
- Study staff will test your urine for infections passed by sex.
- You will get condoms and treatment for infections passed through sex, if needed.
- You will get referrals for other available services if you or your partner(s) need them.

- We will ask for your written permission to get copies of your medical records from other places

You will return for a visit when your test results are available [*insert estimate*]. If results show that you may have some health problems, you may be ineligible for MTN-019. Study staff will refer you to available sources of medical care and other available services. If these problems resolve, you can come back to find out if you are eligible.

Final Screening Procedures/Confirmation of Eligibility:
The screening tests done at this visit will take about [*insert estimate*]. We will:

- Tell you your test results and what they mean.
- Ask questions to update the information from your earlier visits.
- You will have HIV testing with the same procedures as above. If tests show you have HIV, you are not eligible for MTN-019. We will tell you about other studies you may be eligible for, if any, and refer you to medical care and other services.

We then will review all of your screening results. If results show you are eligible for MTN-019, we will fully explain the study to you and answer any questions. If you decide to take part in MTN-019, you will be asked to sign another consent form. *[For applicable sites: You may sign the consent form for further participation in MTN-019 before you finish the screening tests. This gives us permission to do final blood tests for screening and the first set of blood tests for women who enroll in MTN-019 using one blood draw instead of two. We will talk with you more about this if you request it.]*

RISKS AND/OR DISCOMFORTS
Some people feel pain, dizziness, or faintness when blood is drawn. You may have more than expected bleeding, a bruise, swelling, small clot, or infection where the needle goes into your finger or arm. You may feel discomfort during a genital exam. You may have a small amount of vaginal bleeding which will stop shortly after the exam. You may become embarrassed or worried when discussing sex, HIV, and your test results. You may feel worried while waiting for results or if you learn that you have HIV or other infections. Trained counselors will help you deal with any feelings or questions you have. We will make every effort to protect your privacy and confidentiality. Your visits will take place in private. However, it is possible that others may learn of your participation and, because of this, treat you unfairly. For example, you could have problems with your job, family or community. Finding out your HIV status could cause problems between you and your partner. If you have problems, counselors will talk with you and/or your partner to try to help resolve them.

BENEFITS
You may get no direct benefit from the screening tests. However, you will have a physical exam, genital exam, and tests of your liver and kidneys. If tests show you might have health problems, you will be referred for medical care and other available services. You will get counseling and testing for HIV and free condoms. If you have HIV, you will be referred for care, counseling, and other available services. You will get counseling and testing for other infections passed by sex, and treatment, if needed. Your partner(s)

can come here for HIV counseling and testing and treatment for infections passed by sex. For problems not treated here, we will refer you to places where you can get care. If new information is learned about the study or study products, you will be told about this as soon as possible. This study does not provide routine antenatal care; you must have an antenatal care provider to enroll in MTN-019.

You may be withdrawn from screening tests without your consent if:

- You are found to be ineligible for MTN-019.
- MTN-019 stops enrolling new participants.
- The study staff feels that having the screening tests would be harmful to you.
- You are not willing to find out your HIV test result, attend visits or complete screening tests.
- Other reasons, decided by the study staff.

COSTS TO YOU

There is no cost to you for screening tests. Treatments for you and/or your partner(s) for infections passed through sex (other than HIV and hepatitis B and *[insert additional, if applicable, e.g., syphilis]*) are free of charge.

REIMBURSEMENT

[*Sites to insert information about local reimbursement:*] You will receive [$xx] for your time, effort, and travel to and from the clinic at each scheduled screening visit. The study is not able to pay for your routine antenatal care or delivery.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. We will use your personal information, if needed, to verify that you are not in other studies. Study publications will not use your name or identify you personally.

Your records may be reviewed by study staff, as well as:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH) or its study monitors
- the United States Office for Human Research Protections (OHRP)
- [*insert applicable local authorities, e.g., IRB, medicine control authority*]
- the organization that supplies the gels (CONRAD)

[Sites to include/amend the following if applicable:] [*Local/state/national*] regulations require us to report names of people who test positive for [*HIV and other infections*] passed during sex to [*local health authority*]. Outreach workers from [*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 [*health authority*].

[US sites only: In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people not connected with this study,

such as the court system, about your participation or information you give for study purposes. However, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having this Certificate does not prevent you from releasing information about yourself and your participation in the study.]

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] If you are injured, [*institution*] will give you immediate treatment for your injuries. You [will/will not] have to pay for this. You will be told where you can get additional treatment. There is no program to pay money or other forms of compensation through the U.S. National Institutes of Health for such research-related injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about the screening tests, or if you have a research-related injury, you should contact [*insert name*] at [*insert contact information*]. 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*] 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*].

SIGNATURES

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

If required by IRB/EC and reasonably available:

_____	_____	_____
Baby's Father's Name (print)	Baby's Father's Signature/Mark	Date

APPENDIX IV: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT – MOTHER AND INFANT)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-019

Phase 2 Expanded Safety Study of Tenofovir Gel in Pregnancy

[DATE]

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study: Phase 2 Study of Tenofovir Gel in Pregnancy

INFORMED CONSENT
You are being asked to volunteer for MTN-019, a study for healthy, sexually active women who are pregnant with one baby and planning on delivering in a hospital. MTN-019's purpose is to collect more information about the safety of tenofovir gel during pregnancy. The US National Institutes of Health is funding the study. About 384 women and their newborns will join MTN-019 at sites in the US and Africa. We will explain the purpose of the study, risks and benefits to you, and what is expected of you. Please ask questions about anything you do not understand or want to learn more about.

YOUR PARTICIPATION IS VOLUNTARY
This form has information about MTN-019. Once you understand the form, and if you agree to join, you will be asked to sign your name on or mark this form. You will be offered a copy to keep. You do not have to join MTN-019. You may decide not to join, or withdraw any time after signing, without losing regular medical care. If you decide not to join MTN-019, you can join another study later, if one is available and you qualify. If you join MTN-019, you should not join other studies of drugs, vaccines, medical devices or vaginal products for the time you are in MTN-019.

PURPOSE OF THE STUDY
The purpose of MTN-019 is to learn more about the safety of tenofovir gel in pregnancy. MTN-019 will also study how women feel about using the gel and how much tenofovir passes from the gel to the pregnant woman's blood and to the baby's blood. Tenofovir gel is made from the same active drug as tenofovir tablets. Tenofovir tablets are generally safe when used as treatment for HIV. Tenofovir tablets have been tested in pregnant women with HIV infection, and so far have been shown to be generally safe for pregnant women and their babies. HIV-infected pregnant women who take tenofovir tablets before delivery generally have low levels of tenofovir in breast milk.

One study, called CAPRISA 004, found that non-pregnant women who used tenofovir gel before and after sex had a lower risk (39%) of getting HIV, compared to women who used placebo gel (a vaginal gel without tenofovir). Two other studies are testing the effectiveness of tenofovir gel: VOICE (gel used daily) and FACTS 001 (gel used before and after sex). Tenofovir gel is considered experimental at this time, meaning we do not know for sure if it will protect women from HIV. Tenofovir gel is not approved for use in the general community. Tenofovir gel has been tested in 2 other studies in pregnant women so far. In one study called MTN-002, pregnant women received a dose of tenofovir gel before cesarean delivery. No significant health problems were thought to be caused by tenofovir gel for pregnant women or their babies. In this study, tenofovir did pass in low levels to the pregnant woman's blood, uterus, and the umbilical cord blood of babies. Another study called MTN-008 is checking the safety of one week of tenofovir gel used vaginally in pregnant women close to the time of delivery and in breastfeeding women and their babies.

STUDY GROUPS

There are four groups of pregnant women in MTN-019.
Group 1: 114 who are between 36 0/7 weeks and 37 6/7 weeks
Group 2: 90 who are between 28 0/7 weeks and 32 6/7 weeks
Group 3: 90 who are between 20 0/7 weeks and 24 6/7 weeks
Group 4: 90 who are between 12 0/7 weeks and 16 6/7 weeks

In each group, about two out of every three women will receive tenofovir gel and one out of every three women will receive placebo gel. The placebo gel looks and feels about the same as tenofovir gel but does not contain tenofovir or any other medicine. Both gels come in the same kind of applicator. You will be able to find out which gel you got after the end of the study. Until then, no one will be told. Whether you get tenofovir gel or placebo gel will be chosen by lot [or equivalent local term]. You cannot choose or change which gel you get, and the study staff cannot choose or change this for you.

You can only be in one of the four groups. Study doctors will be checking on participant safety as the study continues. Each group will open in the order above, only if safety checks do not show serious risks for participants. You can only join a group that is currently open. All groups use gel for 28 days, unless they need to stop taking gel early.

You are being asked to be in Group *[study site to insert number, as appropriate].*

WHY YOU MAY HAVE TO STOP TAKING THE STUDY GEL EARLY

You will stop taking the study gel early, if you:

- Begin your labor, go to the hospital to have labor induced, or have a cesarean
- Have a miscarriage/pregnancy loss
- Become infected with HIV or hepatitis B
- Are taking medication called PEP for possible recent exposure to HIV infection
- Are found to have certain abnormalities on Pap smear
- Are unable or unwilling to follow study procedures or visit schedule
- Could be harmed by continuing to use gel

STUDY PROCEDURES

If you decide to join the study, your first visit will continue today after you sign or mark this form. Study staff will help you understand the form and answer your questions first. You will give [xx mL] of blood for study staff to keep frozen here while you are in the study. If needed, they will test this blood later to help check on your health. Some women may be offered hepatitis B vaccine, depending on blood test results and if their partner has hepatitis B. We will talk to you more about this if you request it. You will have an ultrasound or have one scheduled for you, if the study doctor thinks this is needed. You should not use spermicides or other vaginal products while you are in MTN-019 (female condoms are allowed).

Your first dose of gel will be here today. You will insert gel in your vagina every day for the next 28 days or until you go into labor, whichever comes first. You will have study visits on Days 7, 14, and 28. You will have a visit 2 weeks after you finish using the gel. You will have more visits after that (about every 4 weeks) until the time of delivery.

You will have a study visit at the time of your delivery if you have used study gel in the 24 hours before you arrived at the hospital. It is important to contact study staff if you think you might be going into labor, or if you are told to go to the hospital for delivery. At the hospital, we will collect some blood from the part of the umbilical cord attached to the afterbirth and some blood (XX mL) from you. We may also measure your baby's weight, length, and head.

You will have a study visit about one month after your pregnancy is over.

At most visits, you will:

- Tell study staff if you had any health problems since your last visit
- Tell study staff about medications and herbal/traditional treatments you are using
- Tell study staff new information on where you live and how to contact you. They will use this information to remind you of visits. If you miss a visit, study staff will try to reach you by [insert]. They will try to reach you through contact people you list. If they talk to these people, they will not say why they want to reach you.
- Answer questions about sexual practices, reproductive health, and gel use. Some of these questions may be asked by computer. If questions are asked by computer, they will be shown on the screen and may be read to you through earphones. You do not need to know how to read to answer the questions. Study staff will show you how to use the computer. You can practice using the computer and ask study staff any questions. Then, you will answer questions using the computer by yourself.
- Have a check of your abdomen, including measurements and baby's heartbeat
- Have a pelvic exam today and on Day 28, including genital swabs to check for normal and abnormal bacteria, signs of inflammation, and changes in the content of vaginal fluid
- Give blood for biomarker tests. This blood will be used for tests to help researchers better understand the immune system, pregnancy and complications

of pregnancy. The immune system is the part of the body that helps protect against and responds to infections. We will ask you to provide separate consent for this at the end of this form. Once available, which will be after the study ends, test results which could be used for the management of your health or medical care will be provided to you, as long as we know how to contact you.
- Get the results of other tests done at your visit and previous visits, for tests that can be used to check on your health.
- Get treatment for some types of infections passed through sex, if you need it
- Get referrals for other medical care and services if you need them.
- Get condoms and panty liners.
- Talk with study staff about using gel and get new supplies of gel.

At your Day 14 Visit, you will also:
- Have blood drawn to test for the amount of tenofovir in the blood
- Use that day's dose of study gel in the clinic (either you or study staff may insert)
- Have another blood test about 1 to 3, 3 to 5, or 5 to 7 hours after you use gel (you will find out today which time period) to see how much tenofovir is in your blood. Blood is drawn for these tests for all participants, because study staff do not find out until the end of the study which participants were using tenofovir gel and which were using placebo gel.

At your Day 28 Visit, you will:
- Have most procedures listed above, except you will not receive any more gel.
- Bring your remaining unused gel applicators to be counted by study staff.
- You will talk with staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex. You will give blood (XX mL) for HIV testing. You will be told your result as soon as it is available (results take [*insert estimate*]). You will talk with us about your results and how you feel about them. Sometimes HIV tests are not clearly positive or negative. In that case, we do more tests until we know your status for sure. You must receive your HIV test results to be in MTN-019. If you have HIV, you are not eligible for MTN-019. We will tell you about other studies you may be eligible for, if any. We will refer you to sources of medical care and other available services.

You will not use any more gel after this visit but you will stay in the study until about 6 weeks after your pregnancy ends.

At your Post-Dosing Follow-up Visits, you will have most of the procedures listed above, except you will not get more study gel. You will have the choice of giving more blood (or not) for biomarker testing at these visits.

Please call the study site at [*SITES TO INSERT NUMBER*] if you think you may be in labor, or if you are going to the hospital to be checked or have your labor induced.

Women who used tenofovir gel in the 24 hours before they arrived at the hospital for delivery will have a Delivery Visit. At the Delivery visit, study staff will:

- Take a sample of umbilical cord blood [site to insert amount] to test for tenofovir. The sample of cord blood will be taken after delivery directly from the placenta (not the baby) once the cord has been cut.
- Take a sample of blood [site to insert amount] to test for tenofovir in your blood.
- Check on your baby's health.
- Look at your medical records and the baby's medical records.

About one month after your pregnancy is over, you will tell us about any medical problems that you or your baby may have had since delivery.

AT ANY TIME IN THE STUDY

If you have health problems that may be from infections passed by sex, you will:

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

If you become infected with hepatitis B, you will:

- Stop using gel, but stay in the study as originally planned.
- Be given referrals for medical care and other services you may need.

If you have health problems, including problems related to your pregnancy, you will;

- Let the study staff know
- Have laboratory tests, physical/pelvic exam and/or ultrasound

If you forget or are unable to bring your unused study gel back to the clinic, study staff may arrange to retrieve the gel from you at home or another location.

If you become infected with HIV, you will stop using gel, but stay in the study as originally planned. If you do not have your unused gel with you, study staff may go with you to your home to collect the gel. Study staff will give you counseling and referrals for medical care and other services available to you, including services for prevention of mother to child transmission of HIV. [*AT MTN-015 SITES: They also will refer you to another study called MTN-015 for women who have become infected with HIV*].

You may be eligible for another research study called MTN-016. If you join the MTN-016 study, information you provide may be shared between this study and the MTN-016 study. We will tell you more about MTN-016, a study which is checking the health of pregnant women who used study products during pregnancy in MTN studies, and the health and growth of their babies up to one year old. For example, we might use ultrasound results from this study for MTN-016 if you join MTN-016.

POSSIBLE FUTURE TESTS

Some blood and vaginal fluids you give during the study may be left over after all study tests are finished. Study staff would like to keep your leftover blood and vaginal fluids. You will be asked to sign another consent form to give permission for that. Even if you do not agree to store blood and vaginal fluids after the study, you can still join MTN-019.

RISKS AND/OR DISCOMFORTS

Whenever your blood is drawn, you may:

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

When you have genital exams, you may feel discomfort in your genital area. You may have slight vaginal bleeding which will stop shortly after the exam.

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

Some, but not all, women who used the gels in other studies have had:

- Dryness, itching, burning feeling, irritation or pain in the genital area
- Vaginal candidiasis (a kind of vaginal infection), discharge and/or gel leaking from the vagina
- Abdominal pain
- Diarrhea

There may also be risks related to your pregnancy or fetus due to study product or procedures that we do not yet know about. One study showed a slightly higher chance of lower weights for babies at one year old, among babies whose mothers used oral tenofovir for HIV treatment when they were pregnant.

Some side effects have been associated with the use of tenofovir tablets, including upset stomach, vomiting, gas, loose or watery stools, weakness, dizziness, depression, headache, abdominal pain, worsening or new kidney damage or failure, inflammation or swelling and possible damage to the pancreas and liver, shortness of breath, rash, allergic reaction (may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, feeling of illness or a potentially serious swelling of face, lips, and/or tongue), bone pain and bone thinning/softening which may increase risk of breakage, and muscle pain and muscle weakness. Your male sexual partners will be protected from potential risks associated with exposure to tenofovir gel through consistent use of approved male condoms during penile-vaginal sex and avoidance of oral-vaginal sex. You could have these effects or other effects that we do not know about.

If you become infected with HIV while using gel, it is possible that tenofovir would not work against HIV in your body. If this happened, it could limit your options for HIV treatment. It is for this reason that you must stop using gel if you become infected with

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

Other Possible Risks:

- If you get the hepatitis B vaccine, you may have side effects related to the vaccine, such as pain at the site of injection or feeling tired.
- We do not know if there are other risks if you use herbal treatments while using gel. Please tell us if you use herbal treatments.
- You may become embarrassed and/or worried when discussing sexual practices, ways to prevent HIV and other infections passed by sex, and your test results. You may become worried while waiting for test results. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality while you are having the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your HIV status could also cause problems between you and your partner. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

BENEFITS

We do not know if tenofovir gel will be proven to work for protection against HIV in the other studies that are testing its effectiveness. Also, the gel you are getting may be placebo gel. You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV prevention. This is true no matter what study group you are in. You will have physical exams and genital exams. You will have tests to check on the health of your liver and kidneys. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you. [*For selected sites only:* If your Pap test result is abnormal, you will be referred for treatment at the [insert name of provider/center].] If your blood tests show that you have never had hepatitis B before, and the study doctor thinks it would benefit you, you may benefit from getting hepatitis B vaccine for free.

You will get counseling and testing for HIV. You will get free condoms. You can bring your partner(s) here for HIV counseling and testing and testing for other infections passed through sex. If you or your partner(s) have infections passed by sex, you will be offered medicine to treat them, if needed. This study does not provide medication for treatment of HIV/AIDS or hepatitis B. If you become infected with HIV or hepatitis B, you will be referred for medical care, counseling, and other services available to you, including services for prevention of mother to child transmission. If you get HIV, you can have HIV testing for your baby here, if it is not otherwise available to you.

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

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

You may be withdrawn from the study without your consent for the following reasons:

- The study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- You are not willing to find out your HIV test results.
- You are not able to attend clinic visits or complete the study procedures.
- Other reasons, decided by the study staff.

If you withdraw early from the study, we will ask you to come in for a final visit with all the exams and tests listed above.

ALTERNATIVES TO PARTICIPATION
You do not have to participate in this or any other research study. [*Sites to include/amend the following if applicable:* There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.]

COSTS TO YOU: There is no cost to you for being in this study.

REIMBURSEMENT: [*Sites to insert information about local reimbursement:*] You will receive [$xx] for time, effort, and travel to and from the clinic at each scheduled visit. *[If applicable, insert reimbursement for calling at the time of labor, and travel to and from specified hospital].*

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

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- the United States Office for Human Research Protections (OHRP)

- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority and names of applicable IRBs/ECs]
- study staff and study monitors
- the organization that supplies tenofovir gel (CONRAD)

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

[US sites only: In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people not connected with this study, such as the court system, about your participation or information you give for study purposes. However, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having this Certificate does not prevent you from releasing information about yourself and your participation in the study.]

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] If you are injured as a result of this study, the [*institution*] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation through the National Institutes of Health for such research-related injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about the study, or if you have a research-related injury, you should contact [*insert name of the investigator or other study staff*] at [*insert telephone number and/or physical address*]. If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization] 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*].

SIGNATURES *[Insert signature blocks as required by the local IRB/EC:]*
If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to have the study, please sign your name or make your mark below. Also, please indicate whether or not you agree to the collection of blood for biomarker testing during the time that you are still in the study but after you are finished using study gel.

___ I agree to the collection of blood for biomarker testing after I am finished using study gel.

___ I do not agree to the collection of blood for biomarker testing after I am finished using study gel.

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

If required by IRB/EC and reasonably available:

_____	_____	_____
Baby's Father's Name (print)	Baby's Father's Signature/Mark	Date

APPENDIX V: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-019

Phase 2 Expanded Safety Study of Tenofovir Gel in Pregnancy

[DATE]

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study:

You have decided to join MTN-019, funded by the United States National Institutes of Health (NIH). While you are in MTN-019, there may be blood or genital fluid taken from you that might be useful for future research. You are being asked to agree to storage of this blood and genital fluid. This consent form tells you about the collection, storage, and use of your blood and genital fluid. Please ask study staff any questions you may have. You will be asked to sign or make your mark on this form to indicate whether you agree to storage and future testing. You will be offered a copy of this form to keep.

HOW WILL YOU GET THE BLOOD AND GENITAL FLUID FROM ME?
You have agreed to have blood and genital fluid collected and tested as part of MTN-019. The study staff would like to keep any leftover blood and genital fluid after MTN-019 is done, to use for future testing. If you agree to this, no additional blood or genital fluid will be taken from you. Only leftover blood and genital fluid will be kept and used for future testing.

HOW WILL YOU USE MY BLOOD AND GENITAL FLUID?
Your blood and genital fluid will only be used to look for additional evidence of infection with HIV or other agents; damage caused by infection; or your body's response to infection. For instance, researchers may look at your blood cells and substances in your blood and genital fluid called proteins and chemicals. They also may look at your genes (DNA), since your genes might affect your response to disease in important ways. Your genes might make you more likely or less likely to become infected, make your responses to infection or to treatment either stronger or weaker, or make HIV progress either more rapidly or more slowly. No other kinds of genetic test will be done by anyone on your stored blood without first explaining the test to you and obtaining your permission. Some of these tests may be done outside of your country.

The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored blood and genital fluid. This is because research tests are often done using ways that are experimental, so the results do not usually help doctors

manage your health. If a rare situation comes up in which the researchers decide that a test result is important for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your contact information. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name and contact information.

Your blood and genital fluid will not be sold or used directly to produce commercial products. Research studies wishing to use your blood and genital fluid will be reviewed by the NIH and a special committee at the researcher's institution (an Institutional Review Board). The role of this committee is to protect you and other research volunteers from harm.

HOW LONG WILL YOU KEEP MY BLOOD AND GENITAL FLUID?
There is no time limit on how long your blood and genital fluid will be stored.

HOW WILL MY BLOOD AND GENITAL FLUID BE STORED?
Your blood will be stored at special facilities that are designed to store samples safely and securely. Some of these facilities are outside of your country. The storage facilities are designed so that only approved researchers will have access to the samples. Some employees of the storage 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.

DOES STORAGE OF MY BLOOD AND GENITAL FLUID BENEFIT ME?
There are no direct benefits to you. The benefit of doing research on stored blood and vaginal fluid includes learning more about HIV infection.

WHAT ARE THE RISKS?
There are few risks related to storing your blood and genital fluid. When tests are done on the stored blood and genital fluid, there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes), it could cause you problems with your family (having a family member learn about a disease that may be passed on in families or learning who is the true parent of a child) or problems getting a job or insurance.

WHAT ABOUT CONFIDENTIALITY?
To keep your information private, your blood and genital fluid will be labeled with a code that can only be traced back to your research clinic. Your name and other personal information will be protected by the research clinic. When researchers are given your stored blood and genital fluid to study, they will not be given your personal information.

The results of future tests will not be included in your health records. Any publication about the results of future tests will not use your name or identify you personally. The researchers will do everything they can to protect your privacy. Every effort will be made

to keep your personal information confidential. However, it is not always possible to guarantee confidentiality. Your personal information may be disclosed if required by law.

[US sites only: In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people not connected with this study, such as the court system, about your participation or information you give for study purposes. However, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having this Certificate does not prevent you from releasing information about yourself and your participation in the study.]

Your records may be reviewed by:
- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- the United States Office for Human Research Protections (OHRP)
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors
- the organization that supplies tenofovir gel (CONRAD)

WHAT ARE MY RIGHTS?
Allowing your blood and genital fluid to be stored is completely voluntary. If you decide not to have any blood and genital fluid stored other than what is needed to complete MTN-019, you can still remain in MTN-019, and your leftover blood/genital fluid will be destroyed. If you decide now that your blood/genital fluid can be stored for future research, you may change your mind at any time. However, you must contact your study doctor or nurse and let them know that you no longer want your samples used for future research. Your blood/genital fluid will not be used and will be destroyed.

WHAT DO I DO IF I HAVE QUESTIONS?
If you have questions about the storage and future testing of your blood and genital fluid, contact [insert the name of the investigator] at [insert physical address and telephone number].

If you have questions about your rights related to the storage and future testing of your blood and genital fluid for research, contact [insert the name or title of person on the Institutional Review Board] at [insert physical address and telephone number].

SIGNATURES

Please carefully read the statements below and think about your choice. No matter what you decide it will not affect your participation in the MTN-019 study or your medical care. Please initial or mark your choice and sign or make your mark below.

[Insert signature blocks as required by the local IRB/EC, yes/no boxes may be used for each specimen type:]

I agree to allow the following leftover samples to be stored for future testing.

_____ Blood

_____ Genital Fluid

OR

_____ I do not agree to allow any of my leftover blood or genital fluid to be stored for future testing.

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

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