

**HPTN 059**  
**Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1%  
Tenofovir Gel**

**A Study of the HIV Prevention Trials Network**

**Sponsored by:**

Division of AIDS, US National Institute of Allergy and Infectious Diseases  
US National Institute of Child Health and Human Development  
US National Institute on Drug Abuse  
US National Institute of Mental Health  
US National Institutes of Health

**Co-Sponsored by:**

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**LIST OF ABBREVIATIONS AND ACRONYMS**

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome AIDS
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
BMD	bone mineral density
BV	bacterial vaginosis
CAB	community advisory board
CBC	complete blood count
CHBV	chronic hepatitis B virus
CDC	Centers for Disease Control and Prevention
CL	(HPTN) Central Laboratory
C <sub>max</sub>	maximum serum concentration
C <sub>max, ss</sub>	maximum serum concentrations at steady state
CORE	(HPTN) Coordinating and Operations Center
CRF	case report form
CRPMC	(NIAID) Clinical Research Products Management Center
CT	<i>Chlamydia trachomatis</i> , chlamydia
DAIDS	Division of AIDS
DSMB	Data and Safety Monitoring Board
EC	ethics committee
EAE	expedited adverse event
EIA	enzyme immunoassay
FDA	(United States) Food and Drug Administration
GC	<i>Neisseria gonorrhoeae</i> , gonorrhea
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HSV-1, HSV-2	Herpes simplex virus type 1, type 2
IND	investigational new drug
IRB	Institutional Review Board
LDMS	Laboratory Data Management System

## LIST OF ABBREVIATIONS AND ACRONYMS continued

LFT	liver function test
LL	local laboratory
mL	milliliter
N-9	Nonoxynol 9
NARI	National AIDS Research Institute
NAAT	nucleic acid amplification testing
NGO	Non-Governmental Organization
NIAID	(United States) National Institute of Allergy and Infectious Disease
PCR	polymerase chain reaction
PK	pharmacokinetic
PMPA	9-[(R)-2-(phosphonomethoxy) propyl] adenine monohydrate
PMPAp	PMPA monophosphate
PMPApp	PMPA diphosphate
PSRT	Protocol Safety Review Team
RCC	(DAIDS) Regulatory Compliance Center
RFP	renal function parameter
RTI	reproductive tract infection
SDMC	(HPTN) Statistical and Data Management Center
SIV	Simian Immunodeficiency Virus
SMC	(HPTN) study monitoring committee
SOP	standard operating procedure
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate (oral tenofovir)
ULN	upper limit of normal
µM	micromole
WB	western blot

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**Investigator Signature Form**

**Final Version 1.0, 17 March, 2005**

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I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study gel for the indication in which it was studied, unless otherwise specified by the Division of AIDS (DAIDS), Gilead Sciences Inc., or the HIV Prevention Trials Network (HPTN) Coordinating and Operations Center. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the FDA is notified that the Investigational New Drug application (IND) is discontinued. Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted to the HPTN Manuscript Review Committee, DAIDS, and Gilead Sciences, Inc. 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 products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

\_\_\_\_\_  
Name of Investigator of Record

\_\_\_\_\_  
Signature of Investigator of Record

\_\_\_\_\_  
Date

**HPTN 059**  
**Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1% Tenofovir Gel**

**SCHEMA**

**Purpose:** To assess the safety of tenofovir gel for vaginal use in HIV uninfected women versus a placebo gel over 24 weeks of gel use

**Design:** Phase II, four arm, two site, randomized, double blind, controlled trial comparing tenofovir 1 % vaginal gel or placebo gel used once daily and tenofovir 1% vaginal gel or placebo gel used prior to intercourse, with 24 weeks of product exposure and follow up. Participants with chronic hepatitis B virus (CHBV) will have an additional 12 weeks follow up.

**Study Population:** US and non-US sexually active, HIV uninfected women with a normal lower genital tract between the ages of 18 and 50

**Study Size:** Approximately 100 participants per site, for a total of 200 women

**Treatment Regimen:**

<b>Arm</b>	<b>Description</b>	<b>N</b>	<b>Frequency</b>
1	Tenofovir gel coitally dependent use	50	Up to two hours before each act of penile-vaginal sexual intercourse to a maximum of twice daily
2	Placebo gel coitally dependent use	50	Up to two hours before each act of penile-vaginal sexual intercourse to a maximum of twice daily
3	Tenofovir gel daily use	50	Once daily at bedtime or longest period of rest
4	Placebo gel daily use	50	Once daily at bedtime or longest period of rest

Participants in Arms 1 and 2 will use the gel before each act of penile-vaginal sexual intercourse (to a maximum of two doses daily). Participants in Arms 3 and 4 will use the gel once daily (before bedtime or longest period of rest).

**Study Duration:** Accrual will require approximately 10 calendar months. Each participant will be followed for up to 24 weeks. CHBV infected participants will additionally return to site at 4, 8 and 12 weeks after completion of gel use. Therefore the entire study should be completed within 19 calendar months.

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**Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1% Tenofovir Gel**

**SCHEMA continued**

**Primary Objective:**

- To assess the local and systemic safety of tenofovir 1% gel for vaginal use in HIV uninfected women versus a placebo gel over 24 weeks of daily and coitally dependent use

**Secondary Objective:**

- To assess the acceptability of, and adherence to tenofovir gel for vaginal use in HIV uninfected women versus placebo gel over 24 weeks of daily or coitally dependent use

**Exploratory Objectives:**

- To measure vaginal flora characteristics, and to descriptively examine changes in these characteristics over the course of prolonged study gel use
- To assess the effects of study gel on cytokine and chemokine expression in cervical secretions
- To evaluate the association between cytokine and chemokine expression
- To correlate cytokine and chemokine expression with colposcopic evidence of inflammation and epithelial disruption

**Study Sites:**

- National AIDS Research Institute (NARI), Pune, India
- Bronx-Lebanon Hospital Center, Bronx, New York, USA

## **1. INTRODUCTION**

### **1.1 Microbicides and Human Immunodeficiency Virus (HIV) Prevention**

While the male condom is effective in preventing sexual transmission of HIV, its use is hampered by deeply rooted cultural and social barriers. About half of all HIV infections worldwide are among women, yet the only available female-controlled method of HIV prevention is the female condom. Alternative prevention tools, such as vaginal microbicides, are urgently needed to slow the rapid spread of heterosexual HIV infection.<sup>1</sup>

Effectiveness trials of vaginal microbicides completed to date have all involved products containing nonoxynol-9 (N-9). Marketed as a spermicide, N-9 is a surfactant, or surface-acting agent, that destroys cellular and microbial membranes.<sup>2,3</sup> Several formulations and various concentrations of N-9 have been tested in humans for safety and effectiveness. Four randomized controlled trials showed that use of N-9 does not protect against HIV infection, and higher doses and more frequent use of N-9 have been linked to increased findings of genital lesions, which increase the risk of HIV infection.<sup>2,3</sup> Therefore, N-9 can not be considered a viable option for HIV prevention.

Tenofovir gel may be an alternative method for preventing HIV transmission. Evaluating the safety of new microbicide candidates such as tenofovir gel is the first step in the critical path to effectiveness trials.

### **1.2 Tenofovir Gel**

Tenofovir is currently approved as antiretroviral therapy in oral form. It is an adenosine nucleoside monophosphate (nucleotide) analog belonging to the class of acyclic phosphonomethylether nucleosides tenofovir, the generic name for the active compound, is interchangeable with its chemical name 9-[(R)-2-(phosphonomethoxy) propyl] adenine monohydrate, or PMPA.

Refer to Sections 1.3 through 1.3.6.2 below, Section 4.1.1, the Investigator's Brochure for Tenofovir Gel (GS-1278) Second Edition, and, the Investigator's Brochure for Viread: Tenofovir Disoproxil Fumarate (PMPA Prodrug) (GS 4331-05) Tenth Edition for additional information on Tenofovir Gel and gel formulation.

### **1.3 Rationale**

Topical agents under development for the prevention of vaginal HIV transmission include non-specific inhibitors of HIV (detergents, acid pH buffering agents, and anti-microbial peptides) and agents that work specifically by inhibiting virus-cell attachment. Another promising approach is using a topical product to block virus replication once infection has occurred. Topical tenofovir gel was chosen to test this approach for a number of reasons, including its activity in target cells for HIV infection (Langerhans-

dendritic cells; monocyte/macrophages, and T cells) of the vagina and cervix and the low frequency of local and systemic toxicity observed in the HPTN 050 phase I study of tenofovir 1% gel. In addition, animal studies have demonstrated that tenofovir gel prevents establishment of systemic infection in macaques when administered prior to or following intravenous challenge with simian immunodeficiency virus (SIV) and that it inhibits vaginal transmission of SIV in macaques.

The goal of this two-center phase II study is to determine the safety of tenofovir 1% gel as a vaginal microbicide over 24 weeks of use, and to gain additional information about the product's acceptability. The HPTN 050 study evaluated 14 days of gel use dosed once or twice daily, (i.e., up to 28 doses). Over 24 weeks, a probable maximum of 168 consecutive daily doses will provide cumulative multiple dose data to assess the long-term safety of tenofovir 1% gel. Additionally, with 24 weeks of gel use, the team intends to identify the length of time beyond two weeks that the participants are willing use the study gel.

The study will be a four-arm, randomized, double-blind, controlled trial, comparing two frequencies of study gel use (daily and coitally dependent) and corresponding study arms in which participants will use a placebo gel. Participants will:

- have pelvic exams with colposcopy and specimen collection for cytokine and chemokine testing
- have blood and urine testing
- have blood pharmacokinetic (PK) sampling
- be provided with and counseled to use water or silicone base lubricated, non-N9 or spermicide containing, male, latex condoms
- be counseled to use the study gel either once daily or with each act of vaginal intercourse up to twice a day, depending on the study arm to which they are randomized

This study will collect data on the use and acceptability of a product that might prove to be effective against HIV and other sexually transmitted infections (STIs) in future larger studies. Information about sexual behavior, including previous vaginal gel use, sexual relationships and negotiation, and use of male condoms, within each site is important background information for proceeding to Phase II/III studies. Moreover, any information obtained about the product's characteristics, packaging, and methods of administration that increases the likelihood that it will be used as recommended for effective protection is relevant to further studies.

### **1.3.1 Justification of 1% Dosing**

Choice of tenofovir gel concentration for the Phase II clinical study is based on the following. First is the demonstration of minimal vaginal irritation in animal and human studies. A rabbit vaginal irritation test identified 1% tenofovir gel as being histopathologically identical to sham or control treatment, while on a qualitative basis 3% gel was more irritating to vaginal epithelia.<sup>4</sup> The tolerability of the 1% gel was confirmed in the HPTN 050 Phase I study, the Phase I dose ranging

study of tenofovir gel (0.3% once daily, then 1.0% once daily, then 0.3% twice daily followed by 1% twice daily). In this study, of the two doses and frequencies studied in the dose finding cohort, the 1% gel applied intravaginally twice daily for 14 days was well tolerated and was identified as the highest practical dose and frequency for further study in subsequent cohorts.

The second line of evidence is from vaginal transmission inhibition studies performed in non-human primates.<sup>4</sup> Six separate studies provided evidence for efficacy of the gel over a range of tenofovir concentrations of 0.3% to 10%. Although the total data are limited and a powered statistical determination as to the efficacy of 1% tenofovir gel versus 0.3% and 10% cannot be made, empirical examination of the efficacy data identifies 1% tenofovir gel as the lowest efficacious concentration tested when given within two hours of infection. See Table 1 summarizing the vaginal transmission inhibition studies of tenofovir gel performed in non-human primates.

Finally, limited vaginal PK tenofovir data in primates and humans demonstrate that tenofovir gel is broadly distributed in vaginal tissues following vaginal application and can penetrate to epithelial tissues.<sup>5</sup> The amount of tenofovir administered by intravaginal application of 4 grams of a 1% dose (40 mg) is comparable to the amount of tenofovir systemically absorbed following ingestion of a 300 mg dose of tenofovir disoproxil fumarate (TDF), the oral form of tenofovir. This dose of tenofovir is highly active against HIV and results in a reduction of plasma HIV ribonucleic acid (RNA) of 1.5 log<sub>10</sub> copies / mL after daily administration for 21 days.

Comparison of the predicted cervicovaginal concentrations of tenofovir gel delivered to those achieved systemically at the standard treatment dose of 300 mg oral TDF, and tenofovir's characteristic prolonged intracellular half-life (diphosphate form, nine to 50 hours depending upon cell type), suggest that an initial and potentially durable barrier to HIV transmission may be possible. In terms of weighing potential risks and benefits, the 1% tenofovir gel minimizes the potential risks of vaginal epithelial toxicity while providing the potential benefit of delivering sufficient tenofovir to achieve an initial and possibly durational barrier to infection.

**Table 1: Use of Topical Tenofovir to Prevent Vaginal Transmission of SIV**

Study	Virus	Number of Exposures	Treatment	Time of administration	Number Infected	Progesterone Pretreatment
1	SIVmac251*	2	1 mL vehicle 10% tenofovir	-24 h, 0 h, 24 h, 48 h -24 h, 0 h, 24 h, 48 h	2 of 2 0 of 4	No**
2	SIVmac251*	1	untreated control 10% tenofovir 1% tenofovir 1% tenofovir	N/A -24 h , -15 m, +24 h -24 h , -15 m, +24 h -15 m	5 of 5 1 of 5 1 of 5 2 of 5	No**
3	SIVmac251*	1	untreated control vehicle 1% tenofovir 1% tenofovir 1% tenofovir	N/A -15 m -15 m - 2 h - 8 h	2 of 5 1 of 5 1 of 5 3 of 5 1 of 5	No**
4	SIVmac251*	1	untreated control vehicle 1 % tenofovir 1 % tenofovir 1 % tenofovir	N/A -15 m -15 m - 2 h - 8 h	4 of 5 2 of 5 1 of 5 1 of 5 2 of 5	No**
5	SIVmac251*	1	untreated control vehicle 1 % tenofovir	N/A - 2 h - 2 h	2 of 5 2 of 5 0 of 5	No**
6	Sivmac251	1	untreated control Vehicle 1% PMPA Vehicle 1% PMPA 1% PMPA	N/A 12 h prior 12 h prior 24 h prior 24 h prior 72, 48, 24 h prior	8 of 8 8 of 8 5 of 8 8 of 8 8 of 8 6 of 8	Yes***

\* All studies were performed with the SIVmac251 isolate of SIV, and female rhesus macaques were inoculated intravaginally. Infections were performed without progesterone pretreatment, except for study six. The indicated studies were performed by 3 independent investigators with studies 2, 3, 4, and 5 being performed by the same laboratory.

\*\*Indian rhesus

\*\*\*Chinese rhesus

h = hours

m = minutes

mL = milliliters



### 1.3.2 Clinical Research

Tenofovir (0.3% and 1%) gel was recently tested in the HPTN 050 Phase I study. In this trial, tenofovir gel was administered intravaginally in four groups of women: sexually abstinent HIV-uninfected and HIV infected women, and sexually active HIV-uninfected and HIV-infected women. The women and their male partners (in the sexually active cohorts) were also asked to assess the acceptability of the product. The study did not include a placebo or comparison arm. Results from the HPTN 050 Phase I study have shown tenofovir 1% gel to be safe and acceptable.

A total of 60 HIV-uninfected and 24 HIV infected women completed the HPTN 050 Phase I study. Safety and acceptability of both formulation were initially tested in the HIV-uninfected, sexually abstinent women at varying doses and frequencies. Since 1% tenofovir gel twice a day was as well tolerated as lower dose/frequency combinations, this regimen was used in sexually active HIV-uninfected and, sexually abstinent/sexually active HIV-infected women. Although 92% reported at least one adverse event (AE) the majority of these events were mild (87%) and limited to the genitourinary tract (77%).<sup>6</sup> Four severe AEs were reported, but only one lower abdominal pain was thought to be product-related<sup>6</sup>.

Of 76 participants who had bacterial vaginosis (BV) evaluation (by using Nugent's score criteria) at both enrollment and Day 14, 30 women had asymptomatic BV at baseline and 15 of them became BV negative after 14 days of tenofovir gel use, while one out of 46 women without BV at baseline had BV detected at 14 days. Overall, 40% of the women had asymptomatic BV at baseline compared to 21% of the women after fourteen days of tenofovir gel use ( $p=0.0005$ ).

Fourteen of 25 women (56%) with PK results had low, but detectable, serum tenofovir levels (limit of quantitation: 3.0 ng/mL) at some point in the 12 hours after dosing on either Day 0 (following the first dose) or on Day 13 (after daily dosing); three of the 14 had detectable levels on both days. The maximum tenofovir concentrations ( $C_{max}$ ) ranged from 3.1 to 25.8 ng/mL, with no clear dose-concentration relationship identified. For the woman with the 25.8 ng/mL level, this peak level occurred 2 hours following the dose; the level rapidly declined to 10.8 ng/mL at 4 hours and was undetectable at 12 hours following the dose. Besides the outlier with the highest tenofovir level, the next highest  $C_{max}$  was 7.1 ng/mL. Considering all women in the PK cohort, the median tenofovir  $C_{max}$  was 3.4 ng/mL (interquartile range: below limit of quantitation [3.0 ng/mL] to 4.7 ng/mL). The median  $C_{max}$  for all subjects (3.4 ng/mL) corresponds to approximately 1% of the maximum ( $C_{max, ss}$ ) and 7% of the minimum ( $C_{24}$  single dose) blood concentrations at steady-state with 300 mg daily oral tenofovir dosing<sup>6</sup>.

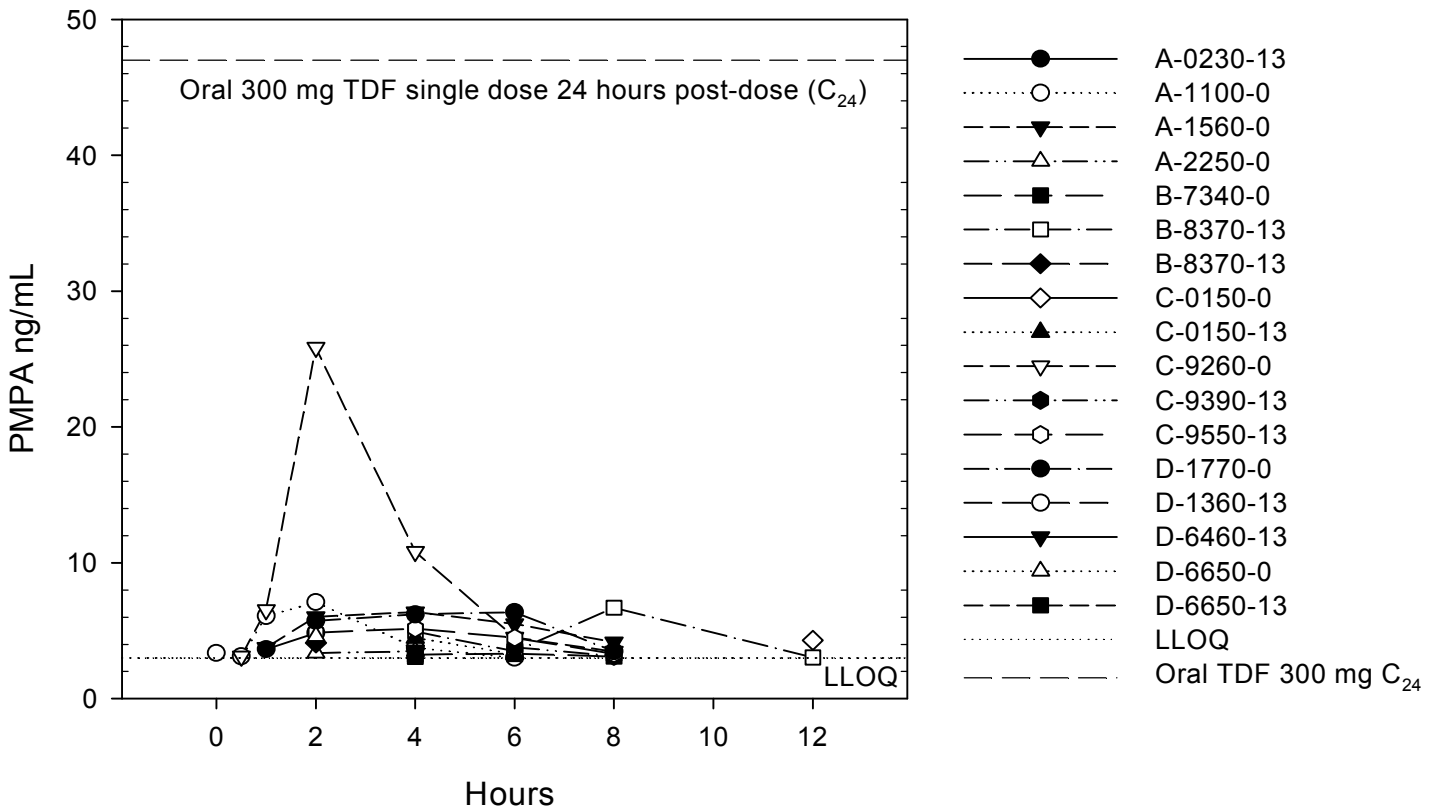
Figure 1 presented below demonstrates tenofovir blood concentration following vaginal administration of 1% tenofovir gel. All levels for all women with measurable tenofovir levels in the blood are shown. (14 of 25; lower limit of

quantitation (LLOQ) approximately 3.0 ng/mL [dotted line]). Legend indicates “cohort” – “ID” – “study day”. For reference the tenofovir level associated with the median 24 hour post-dose blood concentration following an oral 300 mg tenofovir dose is indicated with dashed line.<sup>7</sup>

No clinically significant systemic toxicity was detected. Therefore, it can be concluded that tenofovir 1% vaginal gel used twice daily was well tolerated in abstinent and sexually active HIV uninfected and HIV infected women, with limited systemic absorption and with possible beneficial effects on vaginal microflora. Extended safety and effectiveness studies are warranted based on these initial data.

Additional PK data will be evaluated in this study. Refer to Section 1.3.3 below.

**Figure 1 - Tenofovir Blood Concentrations vs. Time after Vaginal Administration**



First letter = Cohort  
 Cohort A - HIV -uninfected/sexually abstinent  
 Cohort B - HIV -uninfected/sexually active  
 Cohort C - HIV-infected/sexually abstinent  
 Cohort D - HIV-infected/sexually active

4 digits = last 4 digits of participant identifier  
 Last digit = day of study

### 1.3.3 Mechanism of Action/Frequency of Dosing

One of the concerns related to the use of tenofovir as a microbicide in gel form is the uncertainty about how long it will take for the prodrug to be converted to the active antiviral metabolite and therefore how soon after application it can be expected to provide protection during coitus.

Activation of tenofovir is dependent upon anabolic phosphorylation by intracellular nucleoside kinases, whose activity and availability are dependent upon the activation state of the cell. It is unknown how long it will take the lymphocytes, dendritic cells and monocyte/macrophages in the vaginal mucosa to convert the tenofovir to its di-phosphorylated antiviral metabolite. Thus, it is possible that the absolute rate of tenofovir activation will depend upon a wide range of cervicovaginal health factors (e.g., inflammation, stage in menses etc.), as well as the physiochemical properties of the tenofovir gel in the vagina.

Intracellularly, constitutively expressed enzymes convert tenofovir through two phosphorylation reactions to an active triphosphorylated anabolite, tenofovir diphosphate (PMPApp). Tenofovir diphosphate inhibits viral polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination.

Some intracellular nucleoside kinase concentrations, particularly thymidine kinase, which is responsible for the initial phosphorylation reaction of ZDV and d4T, are cell cycle-dependent such that non-proliferating lymphocytes and macrophages express low levels. Because tenofovir is a nucleotide analogue and, therefore, does not require the initial phosphorylation reaction (which is often rate limiting), it may be a more effective inhibitor of HIV in macrophages and other non-dividing cells as compared to some nucleoside analogs.<sup>8</sup>

A number of studies, have indicated that the uptake and metabolism of tenofovir to its active metabolite PMPApp by immune cells is believed to be a rapid process, giving rise to potentially antiviral levels of PMPApp with intracellular half-lives in the 10 to 50 hour range. The IC<sub>50</sub> (50% inhibitory concentrations for tenofovir ranges from 0.04 micromoles ( $\mu$ M) to 8.5  $\mu$ M. Radiolabeled (<sup>3</sup>H) tenofovir is rapidly taken up by resting (3 to 4  $\mu$ M) and activated (1-2  $\mu$ M) peripheral blood mononuclear cells (PBMC), suggesting that cellular uptake is via endocytosis. Endocytosis is a process of cellular ingestion by which the plasma membrane folds inward to bring substances into the cell.

Subsequent metabolism of tenofovir appears to proceed quickly. The mono- and di-phosphate metabolites of tenofovir accumulate rapidly, reaching approximately 0.1 micromolar and approximately 0.3 micromolar, respectively, at six hours after exposure, whereas the PMPA is not detectable (within 0.5 to 24 hours). This suggests that upon entry to the cell, tenofovir is rapidly processed to PMPApp and then to PMPApp, facilitating the formation of a barrier to HIV infection. Therefore, the metabolic properties of tenofovir facilitate the rapid formation and

maintenance of a barrier to virus replication that could hypothetically facilitate its deployment for both coital-associated and coital-dissociated microbicide applications.<sup>8</sup>

Given that tenofovir gel may be effective when administered up to two hours prior to exposure and has a long half life, the suggested timing of coitally associated dosing will be a maximum of twice daily, up to two hours prior to coitus.

#### **1.3.4 Safety**

Given that Phase I data demonstrates measurable plasma concentrations of tenofovir in some participants<sup>6</sup>, participants with CHBV might be at risk for development of tenofovir resistant HBV.<sup>9</sup> Participants with CHBV will be eligible for enrollment; however they will be monitored through HBV viral load, and LFTs.

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 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 the HPTN 050 study show that no new resistance mutations evolved in plasma or cervicovaginal lavage specimens after 14 days of tenofovir gel use. No participant had high level tenofovir mutations (e.g., K65R).<sup>6</sup>

Some of the possible side effects of the study gel are dryness, itching, burning, or pain in the genital area.<sup>6</sup> Refer to Section 8.3 for risks associated with oral tenofovir.

Tenofovir and its oral form (TDF) administered in systemic dose toxicology studies to rats, dogs and monkeys at exposures (based on areas under the plasma concentration curve (AUC)) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density (BMD). The mechanism(s) underlying bone toxicity is unknown. However, systemic absorption of tenofovir from the vaginal gel appears to be minimal, (approximately 1% of the therapeutic oral dose) and the perceived risk of an effect on BMD is low.

#### **1.3.5 Pharmacokinetic Evaluation**

The purpose of this PK evaluation is to evaluate the levels of systemic tenofovir observed among women using gel daily for up to five months.

All women will have phlebotomy at the Week 4, 12 and 20 Visits for PK evaluation of tenofovir in the blood. In order to obtain an assay for one two to six hour timepoint from each participant, participants in the daily dosing arm will be asked to insert their daily study gel dose the morning of the visit, and participants in the coitally dependant arm will be asked to insert a dose the morning of the visit at the Week 20 Visit. PK specimens from participants randomized to the placebo gel arm will not be analyzed.

All PK specimens will be shipped to the HPTN Central Laboratory (HPTN CL) for batched assay. Specimens from each participant receiving daily tenofovir gel from all three PK specimen collections will be evaluated simultaneously at the end of the study.

### **1.3.6 Colposcopy, Cytokine and Chemokine Testing**

Toxicity of the study gel will be evaluated through colposcopic evaluations and by measuring markers of inflammation. Symptoms of genital irritation and product acceptability will be compared to colposcopic findings of epithelial disruption. In addition, cytokine and chemokine levels will be used as surrogate markers of inflammation.

Although an increase in proinflammatory cytokines has been observed in a small human study of N-9,<sup>10</sup> to date, no studies have directly compared genitourinary symptoms, colposcopic epithelial disruption, and proinflammatory cytokines and chemokines. It is anticipated that this study will aid future microbicide studies to more broadly assess toxicity by including cytokines and chemokines as markers of inflammation.

### **1.3.7 Hepatitis B and Tenofovir**

Patients with CHBV have been successfully treated with antiretrovirals which lower Hepatitis B Virus (HBV) viral load and normalize liver enzyme levels. When treatment with antiretrovirals stops, HBV viral load and liver enzyme levels usually rebound.

HBV may develop resistance to antiretrovirals. Over time, the non-resistant viruses decline, but the evolution of resistant HBVs can lead to increased HBV viral load and liver enzyme levels.

#### **1.3.7.1 Hepatitis B Resistance to Tenofovir**

The ability of oral tenofovir to alter HBV replication or engender resistance in HBV co-infected patients undergoing oral tenofovir therapy for HIV infection has not been fully determined. However, we hypothesize that intravaginal administration of tenofovir as a microbicide should result in low serum levels. Studies of patients with HIV and HBV co-infection treated with oral adefovir (a nucleotide drug similar to oral tenofovir, inhibiting the HBV DNA polymerase)

have shown that emergence of resistance is a rare event, occurring in 1.6% of 124 CHBV patients at 96 weeks of therapy.<sup>9</sup>

### **1.3.7.2 Hepatitis B Virus Rebound**

While the systemic absorption of tenofovir from the vaginal gel is small (approximately 1% of the oral therapeutic tenofovir dose), based on experience with oral adefovir and lamivudine, acute exacerbations of hepatitis have been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with Hepsera [adefovir dipivoxil].<sup>11,12</sup>

Therefore, hepatic function should be monitored closely in patients who discontinue anti-hepatitis B therapy. Participants with detectable HBV antigenemia will be monitored at various points throughout the study through HBV viral load tests and liver function tests (LFT). They will return at 4, 8 and 12 weeks after gel use (week 28, 32 and 36 visits) to be monitored for unexpected rebound of HBV levels. If participant agrees, blood specimens will be collected for future resistance testing, these specimens will be collected at baseline, and weeks 12, 24, 28, 32 and 36.

## 2 STUDY OBJECTIVES AND DESIGN

### 2.1 Primary Objective

The primary objective of this study is:

- To assess the local and systemic safety of tenofovir 1% gel for vaginal use in HIV uninfected women versus a placebo gel over 24 weeks of daily and coitally dependent use

### 2.2 Secondary Objective

The secondary objective of this study is:

- To assess the acceptability of, and adherence to tenofovir gel for vaginal use in HIV uninfected women versus placebo gel over 24 weeks of daily or coitally dependent use

### 2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To measure vaginal flora characteristics, and to descriptively examine changes in these characteristics over the course of prolonged study gel use
- To assess the effects of study gel on cytokine and chemokine expression in cervical secretions
- To evaluate the association between cytokine and chemokine expression
- To correlate cytokine and chemokine expression with colposcopic evidence of inflammation and epithelial disruption

### 2.4 Study Design

Phase II four arm, two site, randomized, double blind, controlled trial comparing tenofovir 1% vaginal gel used once daily and tenofovir 1% vaginal gel used prior to intercourse to a placebo gel, with 24 weeks of product exposure and follow up. Participants in all four arms will receive condom counseling and free water or silicone base lubricated, non N-9 or spermicide containing, male, latex condoms on an ongoing basis. The study will be conducted at two sites: New York, USA and Pune, India.

Arm	Description	N	Frequency
1	Tenofovir gel coitally dependent use	50	Up to two hours before each act of penile-vaginal sexual intercourse to a maximum of twice daily
2	Placebo gel coitally dependent use	50	Up to two hours before each act of penile-vaginal sexual intercourse to a maximum of twice daily
3	Tenofovir gel daily use	50	Once daily at bedtime or longest period of rest
4	Placebo gel daily use	50	Once daily at bedtime or longest period of rest

### 2.4.1 Study Visits and Evaluations

Study visits and evaluations are outlined in Section 5 and summarized in Appendix I. Participants will be encouraged (but not required) to bring their male partner(s) with them to any and all study visits, especially Screening and Enrollment visits.

After providing written informed consent, potential participants will be screened for eligibility. During the eligibility screening participants be asked to respond to demographic questions, and will give contact information. They will undergo HIV and STI counseling and testing (pre-test counseling and preliminary testing at the first visit, test results and post-test counseling provided at a later screening visit). They will also undergo a targeted medical history and behavioral screening, urine pregnancy testing, dipstick urinalysis, hematology, LFTs and renal function parameters (LFT and RFP), and HBV testing; a targeted physical exam, and, pelvic exam with Pap smear. The eligibility screening may take place during one visit or may require more than one visit over more than one day. For participants who are presumptively eligible at screening, an Enrollment Visit will be scheduled to take place within 56 days of screening, and at least two days after the end of participant's given menstrual period. Once all screening procedures are complete, and the participant has been provided her test results and appropriate post-test counseling, the enrollment visit may commence that same day, or at a later date up to 56 days post-screening.

At the Final Screening/Enrollment Visit participants will give updated information on their medical and menstrual history; have HIV/STI counseling and testing and, will be questioned on vaginal product behaviors (for pre-use assessment). They will also undergo urine pregnancy testing and dipstick urinalysis. They will give blood for hematology, LFT and RFP, HSV-2, and plasma and serum archive. They will undergo a pelvic exam with colposcopy and cervical and vaginal swab collection for Gram stain, and, cytokine and chemokine testing. Vaginal swabs for quantitative assessment of vaginal microflora will be collected only at the US site since these specimens cannot survive storage for greater than 48 hours. Additionally, participants identified as having CHBV at screening will give blood for HBV viral load testing and, storage for possible future HBV resistance testing. Once all assessments are completed and final eligibility has been confirmed, participants will be randomized into either the once daily or the coitally dependent group, and will receive either tenofovir or placebo gel. They will be provided with:

- Supplies of tenofovir or placebo gel with applicators and, breathable, unscented, non-deodorant, locally available (if possible) panty liners and/or menstrual pads and water or silicone base lubricated, non N-9 or spermicide containing, male, latex condoms for participants' partners
- Instructions for product application
- Instructions to contact the site to report signs or symptoms which are of concern to the participants



Depending on their randomization group, participants will be instructed to insert one dose (the entire contents of one applicator) of study gel into the vagina up to two hours before each act of penile-vaginal sexual intercourse or once daily at bedtime or longest period of rest. Participants in the coitally dependent group will not use study gel more than twice per day.

Follow up visits will be scheduled every four weeks after the Enrollment Visit (based on a 28 day menstrual cycle). After 4, and 12 weeks of study gel use, participants will return for follow up visits. At these visits, participants will give updated information on their medical and menstrual history, be interviewed to assess adherence to the gel use regimen, their sexual practices, study gel acceptability, and ascertain whether any adverse experiences have occurred, and, receive HIV/STI risk reduction counseling (and post-test counseling, if indicated). They will undergo a urine pregnancy test and have a pelvic examination with colposcopy and cervical and vaginal swab collection for Gram stain, and, cytokine and chemokine testing. Vaginal swabs for quantitative assessment of the vaginal microflora only at the US site. They will also give blood for hematology, PK, LFT and RFP testing.

After 8, 16, and 20 weeks of study gel use, participants will return for follow up visits. At these visits, participants will give updated information on medical and menstrual history, be interviewed to ascertain whether any adverse experiences have occurred, and have HIV/STI risk reduction counseling. They will also undergo urine pregnancy testing.

Additionally at the Week 20 Visit participants in the daily use arm will be asked to insert their daily dose the morning of the visit, and participants in the coitally dependant arm will be asked to insert a dose the morning of the visit. A blood draw will be taken for PK testing two to four hours post-dosing.

After 24 weeks of study gel use, participants will stop using study gel, and return to the site for a follow up visit. At this visit participants will give updated information on medical and menstrual history, be interviewed to assess adherence to the gel use regimen and their sexual practices, and ascertain whether any adverse experiences have occurred, be questioned on product acceptability, and have HIV and STI counseling and testing. They will undergo a urine pregnancy test and dipstick urinalysis; have a pelvic exam with colposcopy and cervical and vaginal swab collection for Gram stain, and, cytokine and chemokine testing. Vaginal swabs for quantitative assessment of the vaginal microflora only at the US site. They will give blood for hematology, LFT and RFP, and, plasma and serum archive. During this visit, non-CHBV participants will complete a study burden assessment, and all participants will complete a final acceptability assessment.

The week 24 visit will be the final visit for non-CHBV participants unless there is an unresolved AE. All unresolved AEs continuing at the end of study participation will be followed until resolution or the AE has stabilized (Refer to Section 6.3).

At follow up visits, participants will be asked about douching practices.

CHBV participants will be monitored for exacerbation of hepatitis B infection. HBV viral load will be measured at Enrollment and at weeks 12, 24, 28, 32 and 36. Blood will also be archived from these time points to allow future characterization of HBV resistance. During these visits, participants will give updated information on medical and menstrual history. RFP will also be evaluated at the weeks 28, 32 and 36 visits. On the final Week 36 Visit, a study burden assessment will be administered.

At any of the study follow up visits, or at any ad hoc visits initiated by participants between scheduled visits, abnormalities noted on pelvic exam or menstrual/medical history will be evaluated and followed according to Appendix II; continued/discontinued gel use will be guided by Appendix II.

Participants who are found to have an STI or other reproductive tract infection (RTI) will be offered/referred for counseling, treatment, and follow up care in accordance with the Centers for Disease Control and Prevention (CDC) treatment guidelines. Observed single-dose treatment will be provided whenever possible. Participants with STIs will be encouraged to refer their partners for testing and treatment in accordance with local laws if applicable.

### 3 STUDY POPULATION

A total of 200 sexually active, HIV uninfected women with a normal, lower genital tract (defined by the entry criteria in Sections 3.1 and 3.2 below) will be enrolled in this study. They will be recruited from staff (not supervised by the protocol team staff) and consumers from family planning, STI, postnatal clinics, colleges, and other venues. There are 2 sites, New York, USA and Pune, India. Each site will enroll approximately 100 participants.

Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2 (and the guidelines in Section 3.4). They will be recruited, screened, and enrolled as described in Section 3.3 (and assigned to a study treatment/product/intervention group as described in Section 7.4). Issues related to participant retention and withdrawals from the study are described in Sections 3.5 and 3.6, respectively.

#### 3.1 Inclusion Criteria

Women must meet the following criteria (along with entry criteria to be confirmed at the enrollment visit) determined by participant self report at screening (unless otherwise stated) will be eligible for inclusion in the study:

- be between the ages of 18 and 50 at the time of enrollment as verified according to site standard operating procedure (SOP)
- be willing and able to provide written informed consent (as assessed by a site specific assessment of comprehension) at screening and enrollment
- be in general good health (as determined by the site clinician) at screening and enrollment
- be HIV uninfected (per HPTN HIV Antibody Testing Algorithm, Appendix III) at screening and enrollment
- have a normal Pap test result or are able to document a normal Pap test result in the 90 days prior to screening

*Note: Pap smears will be reported as per the 2001 Bethesda System and will be presumed normal in the absence of intra-epithelial lesion or malignancy.*

- be sexually active, defined as having had penile-vaginal intercourse at least once in the 30 days prior to screening
- be willing to use an effective method of contraception during the study, defined as either a hormonal based method (except vaginal rings); an intrauterine device (IUD) (inserted at least 30 days prior to enrollment); female sterilization; or sexual activity with a partner who had a vasectomy

- be willing to undergo all study related assessments (clinical and laboratory), including speculum examination, colposcopy, urine testing, and blood draws
- be willing to adhere to follow up schedule as required by the protocol
- be willing to use tenofovir gel or placebo gel as required by the protocol
- agree to not participate in spermicide and/or vaginal microbicides study or any other device or drug study while enrolled in the study
- agree to use study provided water or silicone base lubricated, non N-9 or spermicide containing, male, latex condoms for each act of intercourse
- agree to use study provided panty liners and/or menstrual pads for protection from product leakage, while using the study gel if necessary

### 3.2 Exclusion Criteria

Women who meet the following criteria determined by participant self report at screening (unless otherwise stated) will be excluded from the study:

- are menopausal or post menopausal at enrollment

*Note: Menopause is defined as the cessation of menses of 12 calendar months, unless on long acting progestins.*

- have had a hysterectomy
- have a history of adverse reaction to products containing latex
- will use a diaphragm and/or spermicide for contraception
- are taking systemic tenofovir, adefovir or any chronic hepatitis B medications, or plan to while participating in this study
- have a history of adverse reaction to tenofovir and/or adefovir
- have a history of prior participation in this study as indicated by the study site's screening log and participant identification code list

- have a Grade 3 or higher laboratory liver, renal, or hematology abnormality as specified below in accordance with The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) Version 1.0, Dec 2004, with the exception of the creatinine level in order to exclude participants with potential early renal disease.
  - have an absolute lymphocyte count less than 500/mm<sup>3</sup>
  - have an absolute neutrophil count less than 750/mm<sup>3</sup>
  - have Hgb level less than 9 g/deciliter
  - have an decreased platelet count less than 50,000/mm<sup>3</sup>
  - have a decreased white blood cell less than 1,500/mm<sup>3</sup>
  - have aspartate aminotransferase (AST) level greater than 5.0 times upper limit of normal (x ULN)
  - have alanine transaminase (ALT) level greater than 5.0 x ULN
  - have total bilirubin level greater than 2.5 x ULN
  - have alkaline phosphatase (ALP) level greater than 5.0 x ULN
  - have a creatinine level greater than 1.25 X ULN

Normal laboratory values are based on site specific local laboratory (LL) normal reference ranges for the New York site; and on kit normal ranges for the India site.

*Note: CHBV will be defined as a positive hepatitis B surface Antigen (HBsAg) test. CHBV participants will not be excluded from the study. However their status will be captured through hepatitis B screening (at study entry and exit and where clinically indicated), HBsAg, LFTs, HBV viral load tests, and significant medical background history. Blood specimens will be collected for possible future testing for HBV resistance to tenofovir gel.*

- have had a gynecological surgical procedure in the 90 days prior to enrollment
- are pregnant (based on urine pregnancy test at Screening and Enrollment)
- is within 90 days of last pregnancy outcome at enrollment
- have an abnormal pelvic exam finding (observed by study staff, e.g., vulvar, vaginal, cervical and/or perineal ulcer and/or lesion and/or deep epithelial disruption, at screening or enrollment)
- have an STI or RTI according to CDC guidelines, via laboratory tests or on examination, and requiring treatment at screening or enrollment including:

- symptomatic BV
- symptomatic candidiasis
- trichomoniasis
- chlamydia (CT)
- gonorrhea (GC)
- syphilis diagnosed by positive rapid plasma reagin (RPR) positive , confirmed by *Treponema pallidum* hemagglutination (TPHA)
- Herpes simplex virus type 1 (HSV-1)and/or Herpes simplex virus type 2 (HSV-2) (active lesions)
- chancroid
- pelvic inflammatory disease (PID)
- cervical or vaginal warts

*Note: women with genital warts that are located exterior to the labia minora (i.e. labia majora, mons) will not be excluded.*

- genital sores or ulcers
- vaginitis
- cervicitis

*Note: women diagnosed with an STI during screening or in the process of enrollment will be referred/offered for treatment based on site specific capability in accordance with CDC guidelines. Participant will be eligible for enrollment once she has completed treatment and is asymptomatic for the STI. CDC guidelines are available at:*

*<http://www.cdc.gov/STD/treatment>*

*Note: Women who are HSV-2 seropositive will only be excluded if they have active genital herpes (active herpes lesions). Once lesions are resolved, participant may be rescreened for study entry.*

*Note: Signs of asymptomatic BV may include the presence of white to grey homogeneous discharge, positive whiff test (amine odor) with addition of potassium hydroxide (KOH), pH greater than 4.5, presence of clue cells, a decrease in lactobacilli morphotypes, and increase in non-lactobacilli morphotypes. Women with clinical criteria or evidence of BV and with symptoms (symptomatic discharge, odor, itching) will be excluded. Women without symptoms, but with clinical or laboratory evidence of BV, are still eligible.*

- have injected non-therapeutic drugs intravenously in the 12 calendar months prior to enrollment
- have participated in any other spermicide and/or vaginal microbicide study or any device or drug study 30 days prior to enrollment

- have a history of vaginal intercourse more than an average of two times per day in the two weeks prior to screening
- are breastfeeding at screening or enrollment
- have any other condition that, in the opinion of the site investigator, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

### 3.3 Recruitment Process

The study will be conducted at Bronx-Lebanon Hospital in New York USA and NARI, Pune, India.

#### New York

Women will be recruited from staff (except staff supervised by HPTN 059 study staff), and consumers of community-based organizations, student populations from area universities, colleges, clinics, and public gathering places that predominantly serve women.

Recruitment will be conducted via outreach by project staff, and using IRB approved flyers on public kiosks and local newspaper ads if needed. Women who have responded to previous recruitment efforts or from previous studies who may meet eligibility requirements will be contacted by phone or by mail with their prior permission. Recruitment information may be sent to medical staff and case managers at local hospitals and clinical practices to give to provide to women who may be eligible.

Study staff will give talks on microbicides (e.g., medical grand rounds) and videos may be shown at Community Based Organizations (CBO) meetings to increase awareness about microbicide research and more specific recruitment flyers will be handed out at these talks. Specific ideas about recruitment venues and strategies will be sought from local Community Advisory Boards (CAB).

The study will also be listed with the US Department of Health and Human Services (DHHS) AIDS Clinical Trials Service, which is accessible via phone (1-800-TRIALS), and on the internet at [www.actis.org](http://www.actis.org). It will be listed with local websites when feasible.

#### India

Study participants will be recruited mainly from three communities which are part of NARI's community contact program. NARI is collaborating with 3 Non-Governmental Organizations (NGOs), specifically Deepagriha, John Paul Slum Development Program, and Jagruti. The peers working under these NGOs will be given study specific information for participant information. Peers regularly arrange community meetings with men and women which are attended by NARI community educators. Information about the study will be given during these group meetings, and willing and eligible participants will be referred to the study clinic.

Participants will also be enrolled from other sources such as NARI peripheral clinics, and other communities. Specific ideas about recruitment venues and strategies will be sought from local CABs.

IRB approved informational material, such as flyers and booklets, will be developed for community awareness.

### **3.4 Co-Enrollment Guidelines**

Participants will be instructed not to participate in any other spermicide/vaginal microbicide study, or any device or drug study 30 days prior to enrollment and throughout study.

### **3.5 Participant Retention**

With the consent of the participant, clinic staff will obtain contact information from people who would be expected to know the whereabouts of the participant enrolled in this study. The need to attend all scheduled follow up visits must be emphasized to each study participant at every visit. If a participant misses a scheduled study visit, the study site staff will try to establish communication with the participant through all possible means (e.g., telephone, field contact, and writing), without breaching the participant's confidentiality. Study site staff is responsible for developing and implementing site-specific SOPs to achieve complete follow up.

Once participants are enrolled in this study, the study site staff will make every effort to ensure non CHBV participants participation for 24 weeks of follow up, and CHBV participants' participation for 36 weeks of follow up, in order to minimize possible bias associated with loss-to-follow up. Each site will establish participant retention procedures to target an average annual retention rate of 95% at 24 weeks. Study site staff at each site is responsible for developing and implementing site-specific SOPs to target this goal. Suggestions for such procedures include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process, and re-emphasis at each study visit.
- Thorough explanation of the importance of all four study treatment groups to the overall success of the study.
- Collection of detailed locator information at the study Screening Visit, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.



- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow up on missed visits.
- Mobilization of trained outreach workers or “tracers” to complete in-person contact with participants at their homes and/or other community locations.
- Regular communication with the study community at large to increase awareness about HIV/ Acquired Immunodeficiency Syndrome (AIDS) and explain the purpose of HIV prevention research and the importance of completing research study visits.
- Encouraging but not requiring partner involvement at all follow up visits.

### **3.6 Participant Withdrawal**

Regardless of the participant retention methods just described, participants may voluntarily withdraw from the study for any reason at any time. The site investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, DAIDS Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, and HPTN CORE Protocol Specialist.

Participants withdrawn from the study will be accounted for statistically as described in Section 7.6.1.

Unless they withdraw their consent, participants who are randomized into the study who voluntarily discontinue gel use, those who use product but not as advised by study staff, those who discontinue product as advised by the study staff, inject non-therapeutic drugs intravenously once enrolled, or become pregnant will not routinely be withdrawn from the study. Rather, every effort will be made to complete the regularly scheduled safety evaluations, as described in Section 5.9.

Participants who become pregnant during the study will discontinue gel use while they are pregnant; however they will continue with their follow up visits. For any participants who become pregnant during follow up, site staff will offer counseling on options available to the participant, in accordance with site specific SOPs. If a repeat urine pregnancy test is negative after 42 days, the participant may resume study gel use.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or site Institutional Review Board/Ethics Committee (IRB/EC) terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation (as described in Sections 5.5 and 5.6), i.e. at the end of gel use, of participants without chronic HBV

infection (non-CHBV) who terminate from the study prior to week 24, and for CHBV participants who terminate from the study prior to weeks 28, 32, and 36 visits. Study staff will record the reason(s) for all withdrawals from the study in participants' study records.

### **3.7 Male Involvement**

Participants will be encouraged (but not required) to bring their male partner(s) with them to any and all study visits, especially Screening and Enrollment visits. Male partners will be provided information on all study related visit procedures. Male partners may also be contacted at their residence by trained study staff to give study specific information if the male partner of the participant is willing.

## 4 STUDY TREATMENT, PRODUCT, AND INTERVENTION

Tenofovir gel is an investigational drug and consideration should always be given to measures that minimize contact during handling, preparation and disposal procedures.

### 4.1 Drug Formulation

#### 4.1.1 Tenofovir Gel

Tenofovir gel is a clear, transparent, viscous gel packaged in epoxy inner-lined aluminum tubes with a white polyethylene screw cap equipped with a puncture tip. Each tube contains six grams of 1% tenofovir gel (weight/weight) formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, hydroxyethylcellulose, and pH adjusted to four to five. The gel is applied with a polyethylene applicator capable of administering a four-gram (equal to four mL) dose of gel.

Product should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25 degrees Celsius (°C)/ 77 degrees Fahrenheit (°F). Excursions are permitted to 15°C to 30°C (59°F to 86°F).

#### 4.1.2 Placebo

The placebo for this study is the carrier vehicle gel, which is identical to tenofovir gel without the tenofovir component. The placebo gel will be supplied in identically packaged tubes with applicators as the tenofovir gel.

### 4.2 Usage Regimen

Study participants will receive supplies of tenofovir or placebo gel from the study site for use during the study period. All participants will be instructed to start using tenofovir or placebo gel at the time of enrollment and continue using the gel for 24 weeks, however instructions vary according to whether it is used in conjunction with vaginal intercourse (coitally dependent – Arms 1 and 2), or daily (Arms 3 and 4), see Sections 4.2.1 and 4.2.2.

Arm	Description	N	Frequency
1	Tenofovir gel coitally dependent use	50	Up to two hours before each act of penile-vaginal sexual intercourse to a maximum of twice daily
2	Placebo gel coitally dependent use	50	Up to two hours before each act of penile-vaginal sexual intercourse to a maximum of twice daily
3	Tenofovir gel daily use	50	Once daily at bedtime or longest period of rest
4	Placebo gel daily use	50	Once daily at bedtime or longest period of rest

Staff will review and provide instruction for applicator use as needed. Detailed written and oral instructions for the use of either tenofovir or placebo gel according to the protocol will be provided to the participant.

#### **4.2.1 Arms 1 and 2**

Participants will be instructed to insert one dose (the entire contents of one applicator) of study gel into the vagina up to two hours before each act of coitus if possible. The gel can be applied a maximum of twice per day.

#### **4.2.2 Arms 3 and 4**

Participants will be instructed to insert one dose (the entire contents of one applicator) of study gel into the vagina once daily (before bedtime or longest period of rest).

### **4.3 Product Supply**

The current Investigational new drug application (IND) for tenofovir gel is held by DAIDS. Tenofovir gel, placebo and applicators for this study will be provided by Gilead Sciences, Inc.

Site pharmacists will obtain study products from the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC).

Sites will be responsible for obtaining breathable, unscented, non-deodorant panty liners for distribution to the participants, and, water or silicone base lubricated, non N-9 spermicide containing, male, latex condoms, as described in Section 4.3.2, to distribute to participants throughout the study .

#### **4.3.1 Tenofovir gel, Placebo gel and Applicators**

Gilead will manufacture and package Tenofovir gel and placebo gel under good manufacturing practice conditions. Both products will be provided in identically packaged tubes with applicators.

Site Pharmacists will obtain study products and applicators from the CRPMC. The study products will be stored in a secure, limited-access area at the site, at controlled room-temperature.

#### **4.3.2 Condoms, Panty Liners and/or Menstrual Pads**

Water or silicone base lubricated, non N-9 or spermicide containing, male, latex, condoms, and, breathable, unscented, non-deodorant locally available panty liners and/or menstrual pads will be provided by the site for all participants. Male condoms will be promoted for use for all sexual encounters during the study period.

A list of condoms that have been tested to be compatible with tenofovir and the placebo gel will be provided to the study sites.

Panty liners and/or menstrual pads will be provided by the site at enrollment and at each follow up visit during gel use and upon request from the participant, by the study site coordinator or designee. These supplies are provided to participants to assist with product leakage during the study.

Participants will be asked to use study provided menstrual pads and/or panty liners if needed for hygienic purposes and to protect against product leakage. To avoid potential confounding of AE data (e.g., abrasions, changes in vaginal microflora, and allergic reactions to product components) that may be related to menstrual hygiene products (except tampons), participants will be asked to report if they have used any products other than the products provided by the study site staff.

Use of the participant's preferred brand of tampons is acceptable, and is not expected to confound AE data.

#### **4.4 Product Accountability**

The site pharmacist must maintain complete records of all study products (except study provided condoms, panty liners and/or menstrual pads) received from the CRMPC, and subsequently dispensed to study participants.

#### **4.5 Adherence**

Data related to adherence will be collected through the administration of a structured interview including open-ended response options at the Week 4, 12 and 24 visits. The interviewer will ask questions about:

- Condom use
- Frequency of intercourse, product and condom use since the last visit.
- Detailed questions about last sexual act with gel and last sexual act without gel, including:
  - Use of product, and when product was used in relation to coitus, or period of longest rest
  - Use of condoms or other birth control methods
  - Type of partner

Douching history and use throughout the study will be captured on the Case Report Forms (CRF).

##### **4.5.1 Adherence Counseling**

Adherence counseling will be provided to study participants assigned to the four study gel groups upon enrollment into the study, and as needed thereafter to

help ensure high rates of gel use. Counseling will be provided in accordance with standard study methods that will address such topics as client-centered strategies to remember to use the products for each episode of vaginal intercourse or daily (depending on group they are randomized to); to ensure the availability of the products both in the home and away from home; and to negotiate gel use with “primary” and “non-primary” partners. Counseling also will include reminders to contact study staff with questions about gel use and requests for additional supplies. For participants who have adherence problems, every effort will be made to identify adherence strategies to increase their rates of gel use throughout the course of the study.

Participants will be counseled to avoid douching or cleaning the vagina as this will alter exposure to study drug. They also will be instructed to:

- Only use the study gels vaginally
- Not douche or otherwise clean the vagina, or insert other vaginal products, within two hours before and two hours after using study gel (menstruating participants are allowed to use tampons as needed)
- Not use other participants’ study gel
- Not distribute their study gel to other women

*Note: Participant behaviors regarding condom and study gel use data will be collected via standardized interviewer-administered questionnaires developed by the Protocol Team in conjunction with study site staff and community representatives, to maximize the accuracy of self-reported data. In order to minimize “socially-desirable” reporting, these questionnaires will be administered prior to the delivery of HIV/STI risk reduction and adherence counseling.*

#### **4.5.2 Adherence Assessment**

Data on adherence to the gel use regimen will be collected at the Weeks 4, 12, and 24 visits via interviewer-administered questionnaires. These questionnaires will ascertain participants’ frequency of sexual intercourse, condom use, gel use, and stated reasons for non-use. They will be administered prior to the delivery of HIV/STI risk reduction and adherence counseling. The HPTN Study Monitoring Committee (SMC) will monitor adherence rates over time, and adherence counseling methods will be updated if needed to address lower-than expected rates.

#### **4.6 Acceptability Assessment**

A vaginal product behavior assessment will be administered at the Enrollment Visit. Product acceptability will be assessed at Weeks 4, 12 and 24.

The acceptability instrument will collect information on the following categories:

- Participant’s reactions to the gel – likes and dislikes

- Participant's perception of her primary partner's reactions to the gel – likes and dislikes
- Participant's perception of her non-primary partner (if applicable) reactions to the gel – likes and dislikes
- Gel impact on sexual encounter
- Ease or difficulty of use

The final acceptability assessment will be conducted at the week 24 Visit, or at trial discontinuation (which ever comes first). The final assessment will include all the questions on the standard instrument, with some additional questions to probe further on issues that emerge as salient during the course of the trial.

#### **4.7 Concomitant Medications**

Any concomitant medications will be permitted for the participant with the exception of those not permitted under criteria for inclusion and exclusion. All concomitant medications will be reported on the study participants' clinical records and recorded on the CRFs for all medications received as of the first Screening visit, and throughout the study. In addition to prescribed and over-the-counter medications needed, vitamins, herbal remedies, and other traditional preparations will be recorded. Alcohol and recreational or street drug use will be recorded in clinical progress notes if needed for interpretation/documentation of observed participant health status. Medication used for the treatment of AEs that occur during study participation also will be recorded on applicable study CRFs.

To protect the integrity of the lower genital tract and reduce the possibility of AEs due to agents other than the study gel and applicator, spermicides, diaphragms, and contraceptive vaginal rings should not be used during this study. Participants who report current use of these methods of contraceptive products and devices during screening or while enrolled in the study will be counseled regarding the use of alternative methods and referred to family planning services for provision of alternative methods should they enroll in the study. Participants will not be terminated from the study if they report current use of these contraceptive methods or devices while enrolled in the study. Additionally, participants will be encouraged to avoid douching during study participation and to avoid the use of vaginally-applied medications/preparations within two hours before and two hours after having vaginal intercourse.

#### **4.8 Toxicity Management**

In response to AEs reported by study participants and/or observed upon exam by study staff, the study site investigator or designee will recommend either continuation or holding gel use consistent with the criteria in Appendix II. Product use also will be held or discontinued in the event of a expedited adverse event (EAE) that is judged by the site Investigator or designee to be definitely, probably, possibly, or probably not related to the study gel or applicator.

Unless the participant withdraws her consent, she will remain in the study to complete the safety evaluations (unless clinically contraindicated) according to Appendix I, and/or as specified in Appendix II.

#### **4.9 Procedures to be Followed in the Event of Pregnancy**

All participants will be instructed to report pregnancies to site investigator or to the study staff who will in turn report to the site investigator; the site investigator will inform the Protocol Safety Review Team (PSRT - the Protocol Chair and Co-Chairs, study site Investigators, NIAID Medical/Program Officer, a manufacturer representative CORE Protocol Specialist, SDMC Biostatistician, and SDMC Protocol Operations Coordinator or their designees). The site Investigator will counsel the participant and discuss possible risks if the pregnancy is continued according to site-specific SOPs.

Sites will provide water or silicone base lubricated, non N-9 or spermicide containing, male, latex condoms, and, facilitate participants' access to all contraceptive methods. However, in the event of pregnancy, sites will counsel participants and will facilitate access to services, according to the site-specific SOPs.

Participants who become pregnant during the course of the study will discontinue gel use while they are pregnant, and will not routinely be withdrawn from the study. Rather, if the participant does not withdraw her consent, every effort will be made to complete the safety evaluations according to Appendix I, and/or as specified in Appendix II, and will follow the modified study procedures described in Section 5.9.2, until their study exit date or their pregnancy outcome is ascertained, whichever is longer.

If the pregnancy test is negative 42 days after the initial positive pregnancy test, the participant may resume study gel use.

Refer to Section 6.4.1 regarding the reporting of pregnancy outcomes.



## 5 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is presented in Appendix I. Presented below is additional information on visit-specific study procedures. A detailed instruction guide to standardize all study procedures across sites will be provided in the study-specific procedures manual.

### 5.1 Screening Visit (up to Day -56)

After providing written informed consent, potential participants may be screened for eligibility over two or more visits if necessary, and eligibility must be confirmed at the enrollment visit. All evaluations will be completed in a step-wise manner for potential participants who meet the study eligibility criteria. For participants who do not meet the eligibility criteria, screening will be discontinued when ineligibility is determined.

For participants who are found to be presumptively eligible based on the evaluations listed below at these visits, final eligibility will be confirmed at Enrollment Visit scheduled to take place within 56 days of the initial Screening Visit.

#### 5.1.1 Clinical Procedures

- assign participant ID
- explain study requirements to the participant
- administer test of comprehension according to site SOPs
- obtain written informed consent(s)
- collect demographic and locator information
- obtain behavioral eligibility information
- provide HIV/STI pretest, and, risk reduction counseling
- collect medical and menstrual history
- provide counseling on contraceptive options
- perform targeted physical exam
- collect urine for pregnancy testing; GC and CT testing; dipstick urinalysis for protein, glucose and blood; urine microscopy and culture if dipstick is positive for leukocyte esterase or nitrates
- perform pelvic examination including:
  - naked eye exam of external genitalia
  - speculum exam of vagina and cervix
  - collection of pH sample from the vaginal wall
  - collection of swab specimen from the lateral vaginal wall for:
    - two dried smears (Gram stain assessment at the HPTN CL)
    - wet mount for candidiasis, trichomoniasis, and clue cells

- collect genital ulcer swab for multiplex polymerase chain reaction (PCR) (at the HPTN CL) if ulcer or other anogenital finding thought to be herpetic identified
- collection of ecto-and endocervical specimen for Pap smear (unless documentation of a normal Pap smear test result in the 90 days prior to screening is available and provided)
- when clinically indicated:
  - offer/refer for STI treatment
- collect blood for HBsAg test, HIV serology, syphilis serology, HSV-2 serology, complete blood count (CBC), LFT, [ALP, AST, gamma glutamyl transferase (GGT), ALT, total bilirubin], RFP, [blood urea nitrogen, creatinine]
- provide test results when available, with associated post-test counseling

### **5.1.2 Laboratory Procedures**

- perform urine pregnancy test
- perform urine nucleic acid amplification testing (NAAT) for GC and CT
- record results of dipstick urinalysis for protein, glucose and blood (perform microscopy and culture if dipstick is positive for leukocyte esterase or nitrates)
- perform enzyme immunoassay/western blot (EIA/WB) test for HIV
- perform syphilis, HBsAg, and, HSV-2 serology
- perform CBC, LFT and RFP

## **5.2 Final Screening/Enrollment Visit and Baseline Evaluations (Day 0)**

Participants who are found to be presumptively eligible during the screening process will complete an Enrollment Visit post menses, and within 56 days after the initial Screening Visit. Participants who do not complete an Enrollment Visit within 56 days of screening must repeat the entire screening process.

All participants will receive their screening test results at their Enrollment Visit (if not previously received). For those whose test results meet the study eligibility criteria, the procedures below will be undertaken in a stepwise manner to confirm eligibility. As was the case at the Screening Visit, procedures will be discontinued if ineligibility is determined at this visit.

### 5.2.1 Clinical Procedures

- administer test of comprehension according to site SOPs
- obtain written informed consent(s)

*Note: Consent for storage of specimens for future research may be obtained prior to or after enrollment, but must be obtained prior to collection of specimens*

- update locator information

#### **To determine enrollment eligibility:**

- update medical and menstrual history
- collect urine for pregnancy testing; dipstick urinalysis for protein, glucose and blood; urine microscopy and culture if dipstick is positive for leukocyte esterase or nitrates
- perform pelvic exam including:
  - naked eye exam of external genitalia
  - speculum exam of vagina and cervix
  - collection of pH sample from the vaginal wall
  - collection of swab specimen from the lateral vaginal wall for wet mount for candidiasis, trichomoniasis, and clue cells
  - colposcopic examination

#### **Additionally for baseline evaluations:**

- collection of two cervical swabs for cytokine and chemokine testing (for analysis at HPTN CL)
- collection of one cervical swab for one dried smear for detection of neutrophils (Gram stain assessment at the HPTN CL)
- collection of vaginal swab for quantitative vaginal culture (for assessment at the HPTN CL from US site only)
- collection of swab specimen from the lateral vaginal wall for two dried smears (Gram stain assessment at the HPTN CL)

#### **Baseline evaluations:**

- provide HIV/STI pre-test, and, risk reduction counseling
- provide screening test results (if not previously provided), and associated post-test counseling
- collect urine for GC and CT testing
- collect blood for HBsAg, HIV serology, HSV-2 serology, syphilis serology, plasma and serum archive, CBC, LFT and RFP collect blood specimen for HBV viral load (CHBV participants only, for analysis at the HPTN CL)

- collect blood for storage of specimen for possible future HBV resistance testing *if participants have provided written informed consent to have specimens stored for future research* (CHBV participants only)
- administer vaginal product behavior assessment
- provide study gel and instructions for use (with panty liners and/or menstrual pads, and condoms)
- when clinically indicated:
  - offer/refer for STI treatment
- provide test results when available, with associated post-test counseling

### 5.2.2 Laboratory Procedures

- perform urine pregnancy test
- perform urine NAAT for GC and CT
- record results of dipstick urinalysis for protein, glucose and blood (perform microscopy and culture if dipstick is positive for leukocyte esterase or nitrates)
- prepare quantitative vaginal specimen for shipment to HPTN CL (US site only)
- prepare HBV viral load for analysis at the HPTN CL (if applicable)
- perform EIA/WB test for HIV, HSV-2 serology and syphilis serology
- prepare blood specimens for plasma and serum archive
- perform CBC, LFT, RFP and HBsAg
- prepare specimen to archive for possible future HBV resistance testing (if participant has consented to specimen storage)

***Note for all follow up visits: All follow up visits should be scheduled, ideally, on dates (within the visit window) when the participant is not on her menses. If a study visit does occur during the participant's menses, all visit procedures except the pelvic exam, colposcopy, and associated specimen collections (if clinically indicated), should be performed at that time. If indicated, the pelvic exam, colposcopy, and associated specimen collections required for the given visit will be rescheduled for a date as soon as practical (within the visit windows if possible) after the end of participant's menses.***

## 5.3 Weeks 4, 12 Visits

**(Week 4: target day 28, allowable Day 21 – 35)**

**(Week 12: target day 84, allowable Day 77 – 91)**

### 5.3.1 Clinical Procedures

- update locator information
- review study requirements with participant
- administer adherence and acceptability assessments
- provide HIV/STI pre-test, and, risk reduction counseling

- provide test results from previous visit (if not previously provided) with associated post-test counseling
- update medical and menstrual history
- collect urine for pregnancy testing
- collect blood for CBC, LFT and RFP
- collect blood for PK (for analysis at the HPTN CL)
- collect blood for HBV for possible future resistance testing (CHBV participants at week 12 only for analysis at the HPTN CL)
- collect blood for HBV viral load (CHBV participants at week 12 only)
- perform pelvic exam including:
  - naked eye exam of external genitalia
  - speculum exam of vagina and cervix
  - colposcopic examination
  - collection of pH sample from the vaginal wall
  - collection of two cervical swabs for cytokine and chemokine testing (for analysis at HPTN CL)
  - collection of one cervical swab for one dried smear for detection of neutrophils (Gram stain assessment at the HPTN CL)
  - collection of vaginal swab for quantitative vaginal culture (for assessment at the HPTN CL for US site only)
  - collection of swab specimen from the lateral vaginal wall for two dried smears (Gram stain assessment at the HPTN CL)
  - collection of swab specimen from the lateral vaginal wall for wet mount for candidiasis, trichomoniasis, and clue cells
  - collection of swab specimen from the lateral vaginal wall for two dried smears (Gram stain assessment at the HPTN CL)
  - collect genital ulcer swab for multiplex PCR (at the HPTN CL) if ulcer or other anogenital finding thought to be herpetic identified
- provide study gel and instructions for use (with panty liners and/or menstrual pads, and condoms)
- when clinically indicated only (not to be done routinely, specific elements and tests on lists below can be conducted based on clinical judgment. Other tests can be done as needed):
  - collect urine for GC, CT, dipstick urinalysis for protein, glucose, and blood; urine microscopy and culture if dipstick is positive for leukocyte esterase or nitrates
  - collect blood for HIV serology, syphilis serology, HSV-2 serology
  - collect blood for plasma and serum archive
  - offer/refer for STI treatment
- provide test results when available, with associated post-test counseling

### 5.3.2 Laboratory Procedures

- perform urine pregnancy test
- perform CBC, LFT and RFP
- prepare specimen for PK analysis (at the HPTN CL)
- prepare HBV viral load for analysis (at the HPTN CL at Week 12 only for CHVB participants)
- prepare specimen to archive for possible future HBV resistance testing at Week 12 only (if participant has consented to specimen storage)
- when clinically indicated only, perform the following procedures:
  - perform EIA/WB test for HIV
  - perform syphilis, HSV-2 serology, HBsAg
  - perform HBV viral load (if applicable)

### 5.4 Weeks 8, 16, 20 Visits

**(Week 8: target day 56, allowable Day 49 - 63)**

**(Week 16: target day 112, allowable Day 105 – 119)**

**(Week 20: targeted day 140, allowable Day 133 – 147)**

#### 5.4.1 Clinical Procedures

- update locator information
- review study requirements with participant
- provide HIV/STI risk reduction counseling
- provide test results from previous visit (if not previously provided), with associated post-test counseling
- update medical and menstrual history
- collect urine for pregnancy testing
- provide study gel and instructions for use (with panty liners and/or menstrual pads, and condoms)
- when clinically indicated only (not to be done routinely, specific elements and tests on lists below can be conducted based on clinical judgment. Other tests can be done as needed):
  - provide HIV/STI pre-test counseling
  - collect urine for dipstick urinalysis for protein, glucose and blood; and, urine microscopy and culture if dipstick is positive for leukocyte esterase or nitrates
  - collect urine for GC and CT
  - collect blood for HIV serology, HBsAg, syphilis serology, HSV-2 serology, CBC, LFT and RFP
  - collect blood for plasma and serum archive
  - perform pelvic exam including:
    - naked eye exam of external genitalia
    - speculum exam of vagina and cervix
    - collection of pH sample from the vaginal wall

- collect genital ulcer swab for multiplex PCR (at the HPTN CL) if ulcer or other anogenital finding thought to be herpetic identified
  - colposcopic examination
  - collection of swab specimen from the lateral vaginal wall for:
    - two dried smears (Gram stain assessment at the HPTN CL)
    - wet mount for candidiasis, trichomoniasis, and clue cells
  - offer/refer for STI treatment
- provide test results when available, with associated post-test counseling

**Additionally at the Week 20 Visit only:**

- collect blood for PK (for analysis at the HPTN CL)

*Note: Participants will be instructed to apply the study gel in the morning of the Week 20 Visit*

**5.4.2 Laboratory Procedures**

- perform urine pregnancy test
- prepare Week 20 blood specimen for PK analysis (at the HPTN CL)
- when clinically indicated only, perform the following procedures:
  - perform urine NAAT for GC and CT
  - record results of dipstick urinalysis for protein, glucose and blood (perform microscopy and culture if dipstick is positive for leukocyte esterase or nitrates)
  - perform EIA/WB test for HIV
  - perform syphilis, HBsAg, and HSV-2 serology
  - perform CBC, LFT and RFP

**5.5 Week 24/Early Termination Visit  
(target day 168, allowable Day 161 – 175)**

**5.5.1 Clinical Procedures**

- update locator information
- review study requirements with participant
- administer adherence and acceptability assessment
- provide HIV/STI pre-test, and, risk reduction counseling
- provide test results from previous visit when available with associated post-test counseling (if not previously provided)
- update medical and menstrual history

- collect urine for pregnancy testing; GC; CT; dipstick urinalysis for protein, glucose and blood; urine microscopy and culture if dipstick is positive for leukocyte esterase or nitrates
- collect blood for HIV serology, HBsAg, syphilis serology, HSV-2 serology, plasma and serum archive, CBC, LFT and RFP
- collect blood for HBV for possible future resistance testing (CHBV participants only)
- collect blood specimen for HBV viral load (CHBV participants only for analysis at the HPTN CL)
- perform pelvic exam including:
  - naked eye exam of external genitalia
  - speculum exam of vagina and cervix
  - colposcopic examination
  - collection of pH sample from the vaginal wall
  - collection of cervical swab for cytokine and chemokine testing (for analysis at HPTN CL)
  - collection of one cervical swab for one dried smear for detection of neutrophils (Gram stain assessment at the HPTN CL)
  - collection of vaginal swab for quantitative vaginal culture (for assessment at the HPTN CL for US site only)
  - collection of swab specimen from the lateral vaginal wall for two dried smears (Gram stain assessment at the HPTN CL)
  - collection of swab specimen from the lateral vaginal wall for wet mount for BV, candidiasis, trichomoniasis and clue cells
  - collect genital ulcer swab for multiplex PCR (at the HPTN CL), if ulcer or other anogenital finding thought to be herpetic identified
- when clinically indicated only:
  - offer/refer for STI treatment
- provide test results when available, with associated post-test counseling

#### **5.5.1.1 Clinical Procedures (Non-CHBV participants only)**

Non-CHBV participants will have all procedures listed above and:

- administer study burden assessment



### **5.5.2 Laboratory Procedures**

- perform urine pregnancy test
- perform urine NAAT for GC and CT
- record results of dipstick urinalysis protein, glucose and blood (perform microscopy and culture if dipstick is positive for leukocyte esterase or nitrates)
- perform EIA/WB test for HIV
- perform syphilis, HBsAg, and HSV-2 serology
- prepare specimens for blood for plasma and serum archive
- perform CBC, LFT and RFP
- prepare HBV viral load for analysis (at the HPTN CL CHBV participants only)
- prepare specimen to archive for possible future HBV resistance testing (if participant has consented to specimen storage)

### **5.6 Weeks 28, 32 and 36 Visits (After completion of gel use - CHBV Participants Only)** (target day 196, allowable Day 189 – 203) (target day 224, allowable Day 217 – 231) (target day 252, allowable Day 245 – 259)

#### **5.6.1 Clinical Procedures**

- update locator information
- review study requirements with participant
- update medical and menstrual history
- provide HIV/STI pre-test, and risk reduction counseling
- provide test results from previous visit (if not previously provided) when available with associated post-test counseling
- collect blood for HBV viral load and resistance testing
- collect blood for HBV serum archive
- collect blood for LFT
- administer study burden assessment (Week 36 visit only)

#### **5.6.2 Laboratory Procedures**

- perform LFT
- prepare HBV viral load (for analysis at the HPTN CL)
- prepare specimen to archive for possible future HBV resistance testing

## **5.7 Interim Contacts and Visits**

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the Investigator at any time during the study. Participants will have a urine pregnancy test at each interim visit. All interim contacts and visits will be documented in participants' study records and on applicable case report forms.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff or require additional study supplies. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care; all AEs associated with genital symptoms will be evaluated according to the pelvic exam procedures described for the regularly scheduled Follow up Visits, and diagnosis and follow up of any observed abnormalities will proceed according to Appendix II.

## **5.8 Colposcopic Images**

Records of colposcopic images are not required for enrollment and Follow up Visit examinations. The colposcopist will document findings in the participant's chart notes and on the study case report forms. When clinically appropriate, the clinician may choose to retain images in order to complement documentation of baseline findings, abnormal findings or injury.

## **5.9 Follow up Procedures for Participants Who Discontinue Study Product**

Participants who discontinue study product will be encouraged to remain in the study if they are willing, for safety evaluations according to the study follow up schedule with the exceptions described in the following Sections. PK sampling and analysis will not be completed for these participants.

### **5.9.1 Participants Who Seroconvert to HIV**

Study staff will capture seroconversions on study CRFs. All protocol specified procedures will continue except:

- HIV serology
- PK assessments
- Provide study gel
- Counseling for HIV/STI risk reduction. Counseling will be modified to address primary and secondary HIV/STI prevention for infected women

## **5.9.2 Participants Who Become Pregnant**

All protocol specified procedures will continue except:

- Provide study gel
- Bimanual pelvic exam (unless clinically indicated)
- PK assessments

## **5.9.3 Participants Who Become Infected With Hepatitis B**

Participants who are incidentally found to be acutely infected with hepatitis B during the course of the study will not be withdrawn from the study. All protocol specified procedures will continue and the infection will be managed in accordance with current clinical practice at each site. Hepatitis B symptoms will be managed in accordance with conventional clinical practice.

If the participant provides written informed consent, she may be followed according to protocol evaluations for CHVB participants.

## **5.9.4 Participants Who Voluntarily Discontinue Study Gel Use or Miss One or More Follow up Visits:**

All protocol specified study procedures will continue except:

- Provide study gel

*Note: participants who return following missed visit or discontinuation of study gel may resume study gel usage at the discretion of the clinician*

## **5.9.5 Participants Who Discontinue Gel Use Permanently (as advised by study staff):**

All protocol specified study procedures will continue except:

- Study gel dispensing
- PK assessments

## **5.10 Final Contact**

Since participants' week 24 follow up visit will include laboratory testing for HIV and other infections and results may not be available by the week 24 visit, a final contact (in person or by telephone [except for positive HIV test results]) may be required to provide the final study test results, post-test counseling, and treatment. In addition, for participants who become pregnant prior to the study end date, an additional contact may be required to ascertain the participant's pregnancy outcome. Study sites may complete these contacts at the study site or at community based locations, depending on site capacities and site and participant preferences. All final contacts will be documented in participant study records.

A final acceptability and adherence instrument will be administered at the Week 24 visit or study exit visit (whichever comes first). These instruments will be the same as those used during the trial, but will include some additional questions, to probe about overall adherence and acceptability.

### **5.11 Study Burden Assessment**

Participant's perceptions of the burden of study participation will be assessed at study exit. These data will inform on use-adherence, future acceptability, and ethics considerations for future studies. To improve participant's ability to speak freely, questions will be asked by a staff member who has not had previous contact with the participant (if possible).

## **6 SAFETY MONITORING AND ADVERSE EVENT REPORTING**

### **6.1 Safety Monitoring**

Close cooperation among the PSRT and other study team members will be necessary in order to monitor participant safety and respond to occurrences of toxicity in a timely manner.

### **6.2 Clinical Data Safety Review**

Participant safety is of paramount importance to the HPTN. A multi-tiered safety review process will be followed for the duration of this study. The review process, which is both timely and extensive in scope, includes review of medical history information, clinical and laboratory AEs and concomitant medications. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise. Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC Clinical Affairs staff, a PSRT and the sponsor. Additional special reviews may also be conducted at each of these levels as dictated by the occurrence of certain events.

HPTN SDMC Clinical Affairs staff will review incoming safety data on an ongoing basis. Values identified during review that are considered questionable, inconsistent, or unexplained will be queried for verification. AE reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded upon receipt to the DAIDS Medical Officer and SDMC Clinical Affairs staff for review.

The PSRT will aim to meet via conference call every two weeks during the period of study implementation, to review clinical and laboratory data reports (blinded by study treatment) generated by the HPTN SDMC. The content, format and frequency of the clinical data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to the routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary experts external to the HPTN representing expertise in the fields of microbicides, biostatistics, HIV transmission and medical ethics may be invited to join the PSRT safety review. A decision to stop the trial may be made by the PSRT at this time, or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

Decisions regarding permanent discontinuation of study gel in individual participants and in the study overall will be made by the PSRT based on careful review of all relevant data and may involve sponsor consultation with the US Food and Drug Administration (FDA).

In the unlikely event that the protocol team has serious safety concerns that lead to a decision to permanently discontinue study gel for all participants and stop accrual into the study, the protocol team will request an unblinded review of the data by the NIAID Data and Safety Monitoring Board (DSMB) before recommending that the study be stopped. Members of the NIAID DSMB will be independent investigators with no

financial interest in the outcomes of this study. If at any time, a decision is made to discontinue study gel in all participants, DAIDS will notify the US FDA and the Protocol Chairs will notify the responsible IRBs/ECs expeditiously.

Clinical data safety review will be followed according to Section 14.2 of the HPTN Manual of Operations (MOP). The MOP can be accessed on the HPTN website at:

<http://www.hptn.org/web%20documents/HPTNMOP/HPTNMOPTOC.pdf>

### **6.3 Adverse Event Reporting Requirements**

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

Study participants will be provided a 24-hour telephone number and instructed to contact the study clinician to report any AEs they may experience, except for life-threatening events, for which they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek medical care where the study clinician is based, and to request that the clinician be paged or otherwise contacted upon their arrival. With appropriate permission of the participant, whenever possible records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study case report forms. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

For participants who develop any colposcopic abnormality, they will be followed until resolution of the AE. Sites selected for this study will have the capacity and expertise to perform colposcopies independent from the study and will be able to provide follow up care for participants after the study, when necessary.

Participants will be instructed to report problems experienced by male partners to the study clinician, who may suggest follow up care or a referral for such care.

Study site staff will document on study CRFs all AEs reported by or observed in enrolled study participants during the 24 weeks of gel use regardless of severity and presumed relationship to study gel or applicators. Study site staff will document on study CRFs all AEs reported by or observed in CHBV participants during their additional 12 weeks of follow-up after gel use. All AEs will be graded using the DAIDS AE Grading Table Version 1.0, Dec 2004, (also referred to as the "Toxicity Table").

The investigator or designee will assess the relationship of all AEs to the study gel based on the Manual for Expedited Reporting of Adverse Events to DAIDS, the Investigator's Brochure, and his/her clinical judgment.

## 6.4 Expedited Adverse Event Reporting Requirements

The EAE reporting requirements and definitions for this study and the methods for expedited reporting of AEs to the DAIDS Regulatory Compliance Center (RCC) Safety Office ([RCCSafetyOffice@tech-res.com](mailto:RCCSafetyOffice@tech-res.com)) are defined in “The Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual) **dated May 6, 2004**. The DAIDS EAE Manual is available on the RCC website: <http://rcc.tech-res-intl.com>.

AEs reported on an expedited basis must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) available on the RCC website: <http://rcc.tech-res-intl.com>.

### 6.4.1 EAE Reporting Requirements for this Study

#### EAE Reporting Level

This study uses the Intensive Level of expedited AE reporting as defined in the DAIDS EAE Manual.

#### Study Agents for Expedited Reporting to DAIDS

The study agent that must be considered in determining relationships of AEs requiring expedited reporting to DAIDS are tenofovir 1% gel/placebo, and the study agent delivery applicators.

#### Grading Severity of Events

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December, 2004, must be used and is available on the RCC website at <http://rcc.tech-res-intl.com/>.

#### EAE Reporting Periods

AEs must be reported on an expedited basis at the Intensive Level during the Protocol-defined EAE Reporting Period, which is:

The entire study duration for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason); and for a period of 12 weeks after gel use. Thereafter, pregnancy outcomes that meet criteria for expedited AE reporting (e.g., fetal losses) occurring among participants known to be pregnant at Week 24 will be reported.

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.

Information on all AEs experienced by study participants will be included in reports to the FDA and other applicable government and regulatory authorities. Site staff will report information on AEs to the IRB/ECs in accordance with all applicable regulations and site-specific IRB/EC requirements.

## **6.5 Study Monitoring Committee Review**

The HPTN SDMC will prepare study progress reports and reports of AEs experienced by study participants (blinded to treatment assignment) for review by the HPTN SMC. The SMC will conduct interim reviews of study progress (blinded to treatment assignment), including rates of participant accrual, retention, rates of adherence to study gel use, and product safety. These reviews will take place approximately every 90 days, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.



## **7 STATISTICAL CONSIDERATIONS**

### **7.1 REVIEW OF STUDY DESIGN**

The primary aim of this Phase II study is to assess the incidence of vulvar, vaginal and cervical epithelial disruption, erythema and inflammation. These signs as well as symptoms including intermenstrual bleeding, dysuria, and irritation will be collected by symptom review and visual examination of the reproductive tract during a speculum examination in all women during 24 weeks of follow up. Participants who have signs of epithelial disruption detected by naked eye and/or colposcopic examination will be followed according to Appendix II. Because genital infection can cause formation of genital ulcers, inflammation and enhance cervical friability, testing for a range of infections will be performed concurrently with colposcopic examination if clinically indicated. HIV uninfected women participating in one of four treatment arms, following a coitally dependent or once daily regimen for 24 weeks, will be evaluated to assess the safety and effect of tenofovir 1% gel over the treatment period.

### **7.2 Study Endpoints**

#### **7.2.1 Primary Endpoints: Safety/Toxicity**

The safety/toxicity primary endpoints associated with the primary objective of this study are as follows:

- macroscopic evidence of damage (judged not to be due to pathogen or iatrogenic trauma) to the cervical epithelium, and, vulvar and/or vaginal epithelium, including ulceration and other lesions, severe erythema, and/or severe edema, judged as definitely, probably, possibly, or probably not related to the study gel or applicator
- laboratory evidence of Grade 3 or higher toxicity for hematology, liver or renal function as defined by the DAIDS AE Grading Table Version 1.0, December 2004, which cannot be directly attributed to another cause after consultation with the protocol chairs, the study site investigator, and the DAIDS Medical Officer, and judged as definitely, probably, possibly, or probably not related to the study gel or applicator

#### **7.2.2 Secondary Endpoints: Adherence and Acceptability Endpoints**

The secondary objectives of this study are as follows:

- Adherence to the study gel regimen will be assessed by an interview-administered questionnaire at the weeks 4, 12 and 24 visits. Summary measures of gel and condom use over time will be compared between study arms (refer to Section 4.5)

- Acceptability of the gel will be evaluated by an interview administered questionnaire at enrollment (for vaginal product behavior assessment) and weeks 4, 12 and 24. Reasons for voluntary discontinuation and non-compliance related to study gel use will be recorded and compared between study arms (refer to Section 4.6)

The expanded safety data collected by colposcopy examination and vaginal flora and cytokine and chemokine specimens are part of the exploratory objectives of the study.

### **7.3 Accrual, Follow up, and Sample Size**

Per entry criteria described in Sections 3.1 and 3.2, the recruitment target will be:

- 200 HIV uninfected women whose self reported sexual activity is at least once in the 30 days prior to screening, but not more than twice per day in the 14 days prior to screening

Approximately 100 women will be recruited per site. Each study site will target enrollment of 100 study participants over the course of a ten calendar month accrual period, according to the following schedules of monthly enrollment targets.

- Study month 1: 7 women
- Study month 2: 7 women
- Study month 3: 7 women
- Study month 4: 7 women
- Study month 5: 12 women
- Study month 6: 12 women
- Study month 7: 12 women
- Study month 8: 12 women
- Study month 9: 12 women
- Study month 10: 12 women

Each enrolled woman will be followed for 24 weeks. CHBV participants will return to site at 4, 8 and 12 weeks after completion of gel use (Weeks 28, 32, and 36 Visits). Therefore, the entire study should be completed within 19 calendar months.

Each site will target retention of 95% of enrolled participants over the 24 week follow up period.

## **7.4 Random Assignment**

Women will be randomized to one of the four arms. The SDMC will provide each study site with the randomization assignments. Using an unblinded list of product codes and assigned products, the pharmacist at each site will supply each participant with either the active gel or the placebo gel.

Once randomization has been assigned, study site staff will provide information to women on frequency of use (i.e. daily or coital).

## **7.5 Blinding**

Throughout the period of study implementation and data analysis, neither study staff nor participants will be informed of the participants' random assignments. Both study gels will be supplied in identical, single-use tubes, and single use applicators packaged in individual wrappers. Study staff and participants will be unblinded after all study visits and data analyses are completed. Individual exceptions may be considered by the Protocol Chair and Medical Officer in situations where product information may be needed to protect the safety of the participant.

## **7.6 Data Monitoring and Analysis**

### **7.6.1 Safety Analysis**

The primary aim of the study is to assess the local and systemic toxicity of two frequencies of use, daily and coitally dependent, application of tenofovir 1% gel versus a placebo gel among HIV uninfected women. The placebo gel provides information regarding signs, symptoms and/or morbidity that may be attributed to normal variation and/or the study procedures or use of applicator rather than the investigational product being studied. Primary data analyses will tabulate the number of primary endpoints observed during the study, by frequency of use and product assignment within frequency of use. All participants who enroll in the study will be included in each tabulation. Individual participants will contribute once to the calculation of event rates.

The proposed total sample size is N=200, 4 arms of 50 women. For a given arm, if the true rate of a given toxicity endpoint is 5%, 50 women per arm provide 83% power to exclude toxicity endpoint rates greater than 16%, where the safety and toxicity endpoint for a woman is defined as:

- (1) having at least one grade 3 or higher adverse experience during follow up judged by the investigator to be definitely, probably, possibly, or probably not related to the study gel or applicator, or;

- (2) having at least one macroscopic finding or other clinical evidence of damage during follow up (judged not to be due to pathogen or iatrogenic trauma) to the vulvar and/or vaginal epithelium and/or cervical mucosa including ulceration and other lesions, severe erythema, and/or severe edema judged definitely, probably, possibly, or probably not related to the study gel or applicator

For a given frequency of use, safety and toxicity rates of placebo and active gels will be formally compared. Fifty (50) women per arm will assure with 74% power that a 95% confidence interval for the difference between the placebo and active gel toxicity rates has an upper limit no more than 10% when the true toxicity rates for placebo and active gel are both 5%.

Upon enrolling in the study, female participants will be assigned at random to use either the active gel or the placebo gel. Randomization will be stratified by site to ensure equal balanced assignment to each product at each site. Women lost to attrition and/or off study gel will not be replaced; however every effort will be made to complete their regularly scheduled safety evaluations. Two primary analysis datasets will be used for these analyses. The first dataset will be consistent with the intention-to-treat principle in order to preserve the initial benefit of randomization. A randomized woman will be excluded from this dataset only under the following circumstances:

1. If she does not satisfy a major entry criterion (as defined in the statistical analysis plan), or;
2. If study gel was never distributed to her and no data were collected post-randomization

The second dataset will be a subset of the full analysis dataset and will include women that are compliant with the protocol. A randomized woman will be excluded from this dataset only under the following circumstances:

1. If she does not satisfy certain entry criteria (as defined in Sections 3.1 and 3.2), or;
2. If study gel was never distributed to her and no data were collected post-randomization, or;
3. If she has failed to adhere to the study gel regimen (non adherence defined in statistical analysis plan), or;
4. If she was off study gel, because of pregnancy or other reasons (e.g., IV drug use during follow up), for more than a certain proportion of total follow up time (proportion defined in statistical analysis plan)

Events reported during gel use will be analyzed separately from events reported during the 12 weeks post-gel use.

*Women off study gel and/or non-adherent that are included in the full analysis dataset will potentially lower the rate of safety endpoints in the active gel arms. Therefore, the 'per protocol' dataset will be used to explore the sensitivity of the conclusions obtained with the analyses based on the full analysis dataset.*

### **7.6.2 Analysis of PK Data**

Blood levels of tenofovir will be evaluated after vaginal administration. Specimens from participants receiving placebo gel will not be assayed. A single tenofovir blood level will be drawn at the Week 4, 12 and 20 visits. The analysis will be performed in an exploratory way by investigating plasma concentrations of tenofovir during the peak absorption period following dosing (week 20, approximately 2-6 hours post-dose, the period coinciding with peak concentrations in previous studies [HPTN 050]) and much later is the dosing interval during terminal elimination (weeks 4 and 12, approximately 12-16 hours post-dose). Tenofovir blood levels will be further investigated by correlating serum tenofovir levels with HSV-2 serostatus, the presence or absence of genital tract inflammation, and frequency of sexual activity.

### **7.6.3 Analyses of Adherence, Study Gel and Condom Use and Sexual Behavior**

The proportion of women with no coital activity in the last seven days will be computed. These monthly rates will be presented in tables by (1) study arm and (2) study arm by site. Appropriate statistical tests will be used to compare study arms within frequency of use.

Also, for each woman with at least one sexual vaginal act during the 24 weeks of study gel use, the four following proportions will be computed:

- Number of acts protected by condom only divided by the total number of coital acts
- Number of acts protected by study gel only divided by the total number of coital acts
- Number of acts protected by study gel and condoms divided by the total number of coital acts
- Number of acts unprotected by study gel and unprotected by condoms divided by the total number of coital acts

Appropriate summary measures of these four proportions will be presented in tables by (1) study arm and (2) study arm by site. Appropriate statistical tests will be used to compare study arms within frequency of use.

Finally, the proportion of women off study gel at each study month will be computed. These monthly rates will be presented by (1) study arm and (2) by study arm and site. In addition, a table describing the reasons for discontinuation of study gel will be presented by (1) study arm and (2) by study site.

#### **7.6.4 Analysis of Acceptability Data**

Assessment of the acceptability of the gels will be done at enrollment (to assess pre-use vaginal product behavior) and weeks 4, 12 and 24. For these visits, the primary measure of acceptability will be defined as the proportion of women indicating that they would use the gel that they are currently using if it was found to prevent HIV. This measure of acceptability will be presented, for Weeks 4, 12 and 24, in a table by (1) study arm and (2) by study arm by site. Formal statistical comparisons between study arms within frequency of use will be performed only for the study exit visit.

## 8 HUMAN SUBJECTS CONSIDERATIONS

### 8.1 Ethical Review

This protocol and the template informed consent form(s) contained in Appendix IV — and any subsequent modifications — will be reviewed and approved by the HPTN Protocol Review Committee and DAIDS Prevention Science Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent form, participant education, outreach and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible IRBs/EC will review the protocol at least annually. The site Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within 90 days of 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. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office, via the HPTN CORE, in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

Participants who seroconvert during the course of this study will have the option of returning to the clinic for the scheduled visits and continue to receive counseling and support services from site staff when and where available, but will be off study gel.

This study will identify persons who are infected with HIV, either as part of the study screening process or during follow up of enrolled participants. Study staff will provide participants with their HIV test results in the context of post-test counseling. They also will refer persons found to be HIV infected to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV infected persons. Persons found to be HIV infected will be encouraged to refer their partners for testing and treatment in accordance with local laws if applicable.

For any participants who become pregnant during follow up, site staff will offer counseling on options available to the participant, in accordance with site-specific SOPs.

Condom use will be promoted and encouraged to all participants throughout this study.

For participants who develop any colposcopic abnormality, they will be followed until resolution of the AE. Sites selected for this study will have the capacity and expertise to perform colposcopies independent from the study and will be able to provide follow up care for participants after the study, when necessary.

### **8.1.1 Prisoner Participation**

HPTN 059 does not meet the criteria for prisoner participation per US 45 Code of Federal Regulations (CFR) 46.306 (a)(2)(D). HPTN 059 is not suitable for further reviews by local IRBs for the inclusion of prisoners.

## **8.2 Informed Consent**

Written informed consent will be obtained from each study participant prior to the initiation of any study procedures. Each study site is responsible for developing study informed consent forms and a test of the participant's comprehension of the study for local use, based on the informed consent form samples in Appendix IV, which describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable US regulations and local guidelines. The study site also is responsible for translating the template form into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Literate participants will document their provision of informed consent by signing their informed consent forms. Non-literate participants will be asked to document their informed consent by marking their informed consent forms (e.g., with an X, thumbprint, or other mark) in the presence of a literate third party witness. Further details regarding DAIDS requirements for documenting the informed consent process with both literate and non-literate participants are provided in the DAIDS SOP for Source Documentation. Any other site-specific IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

Participants will be provided with a copy of their informed consent form if they are willing to receive it. Study staff will document the informed consent process as described in the Study-Specific Procedures Manual.

Both sites will have a CAB, and obtain input and feedback from the CAB. Protocol team members will work with study staff and community representatives to develop locally-appropriate information materials about the study and a standardized approach to the informed consent process to be implemented at all study sites.

These materials will include information to be made available to male partners. Although each woman will be encouraged to inform male partners about her participation in the study, partner consent, assent or approval will not be required.

## **8.3 Risks**

Participants may experience discomfort when having pelvic exams and/or phlebotomy for this study. During phlebotomy, they also may feel dizzy or faint, or develop a bruise, swelling or infection where the needle is inserted. Participants also may become embarrassed, worried, or anxious while waiting for their HIV and STI test result. Trained counselors will be available to help participants deal with these feelings.



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 discriminated against, or could have problems being accepted by their families and/or communities.

Administration of tenofovir gel intravaginally at 0.3% and 1% concentrations in the HPTN 050 Phase I study resulted in minimal local irritation and little or no systemic adverse effects were identified. Although 92% of participants reported at least 1 AE, 87% of those reported AEs were mild, and 77% of the AEs were limited to the genitourinary tract. Four severe AEs were reported, with only one, lower abdominal pain, thought to be product-related<sup>6</sup>. Therefore the risks associated with tenofovir gel are believed to be less than those identified for systemic use.

In the HPTN 050 Phase I study of tenofovir gel, serum PK analysis in a subset of participants demonstrated that there is no clinically significant systemic toxicity. Fourteen of 24 women with PK results had low, but detectable, serum tenofovir levels.<sup>6</sup> (Refer to Section 1.3.1)

Given that Phase I data demonstrates measurable plasma concentrations of tenofovir in some participants, participants with CHBV might be at risk for development of tenofovir resistant HBV.<sup>6</sup> Participants with CHBV will be eligible for enrollment; however they will be monitored through HBV viral load, and LFTs.

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 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 the HPTN 050 study show that no new resistance mutations evolved in plasma or cervicovaginal lavage specimens after 14 days of tenofovir gel use. No participant had high level tenofovir mutations (e.g., K65R).<sup>6</sup>

Some of the possible side effects of the study gel are dryness, itching, burning, or pain in the genital area. The following side effects have been associated with the use of oral tenofovir:<sup>4,13</sup>

- Upset stomach, vomiting, gas, loose or watery stools
- Dizziness
- Abdominal pain
- Lack of energy
- Kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas
- Shortness of breath
- Rash
- Low phosphate

- Increase of LFTs in children
- Allergic reaction, which may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath or a general feeling of illness
- Changes in bone growth and strength were seen in study animals given tenofovir. It is unknown if taking tenofovir for a long time will cause bone abnormalities in adults. In children, some decrease in bone thickness (density) has been seen

Tenofovir and its oral form (TDF) administered in systemic dose toxicology studies to rats, dogs and monkeys at exposures (based on areas under the plasma concentration curve (AUC)) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density (BMD). The mechanism(s) underlying bone toxicity is unknown. However, systemic absorption of tenofovir from the vaginal gel appears to be minimal, (approximately 1% of the therapeutic oral dose) and the perceived risk of an effect on BMD is low.

There have been other side effects in patients taking the oral form of tenofovir (TDF). However, these side effects may have been due to other medicines that patients were taking or to the illness itself.<sup>14, 15</sup>

Although the oral form of tenofovir is labeled as a Pregnancy Category B agent, it is not definitively known if tenofovir gel has any effect on pregnancy, whether it has any effect on the fetus, or if it is secreted in breast milk. Participants will be counseled on the importance of not becoming pregnant during the study. If the participant does become pregnant during the study, gel use will be stopped and study staff will discuss the choices available to the participant. They will continue with their follow up visits through their originally scheduled study exit date or until their pregnancy outcome is ascertained, whichever is longer.

This and future studies of tenofovir gel are needed to more fully assess the risk profile of topical administration since it is possible that tenofovir gel could cause any of the effects listed above or other adverse effects not reported previously, including effects leading to death or permanent disability. The latter outcomes are unlikely, but may occur due to low levels of systemic drug absorption after topical exposure and to the rarity of severe allergies.

#### **8.4 Benefits**

There may be no direct benefits to participants in this study. However, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of a safe and effective microbicide that prevents sexual transmission of HIV.

In addition, participants will receive HIV/STI counseling and testing as part of the study screening process. Participants will also have pelvic exams and colposcopies. Participants will also have blood and urine tests for a number of STIs, and will be provided with STI treatment if applicable. (Refer to Appendix I, Schedule of study Visits and Evaluations)

## **8.5 Incentives**

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

## **8.6 Participant Confidentiality**

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

Participants' study information will not be released without the written permission of the participant, except as necessary for monitoring by NIAID and/or its contractors (e.g., the DAIDS monitoring contractor), Gilead Sciences, representatives of the HPTN CORE, the HPTN CL and/or SDMC, the FDA, and other regulatory authorities. In addition, for the participant's from India, study related information may be released to the Drug Controller General of India and the Indian Council of Medical Research if necessary.

A Federal Certificate of Confidentiality will be sought for this study. The Certificate applies in the US only (i.e. the New York site) and will protect study staff from being compelled to disclose study related information by any Federal, State or local civil, criminal, administrative, legislative, or other proceedings.

## **8.7 Communicable Disease reporting**

Study staff will comply with all applicable local requirements to report communicable diseases including HIV identified among study participants and their partners (if obligated by local law) to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process. For participants from India, study related information may be released to the Drug Controller General of India and the Indian Council of Medical Research if necessary.

## **8.8 Access to HIV-Related Care**

### **8.8.1 HIV Counseling**

HIV pre-test, risk reduction, and post-test counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled participants at each follow up HIV testing time point. Counseling will be provided in accordance with a standard study counseling manual, and will emphasize the unknown efficacy of the candidate microbicides in preventing HIV infection.

In accordance with the policies of the US National Institutes of Health, participants must receive their HIV test results in order to take part in this study.

Water or silicone based, non N-9 or spermicide containing, male, latex condoms will be provided to participants for use throughout the duration of their participation.

### **8.8.2 Care for Participants Identified as HIV-Infected**

This study will identify persons who are infected with HIV, either as part of the study screening process or during follow up of enrolled participants. Study staff will provide participants with their HIV test results in the context of post-test counseling. They also will refer persons found to be HIV infected to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV infected persons. Persons found to be HIV infected will be encouraged to refer their partners for testing and treatment in accordance with local laws if applicable.

For any participants found to be newly HIV infected who also become pregnant during follow up, every effort will be made to facilitate access to single-dose nevirapine (and/or other interventions) to reduce the probability of HIV transmission to the participant's infant.

Participants seroconverting for antibodies to HIV will be counseled appropriately. They will be encouraged to return for follow up visits, but will be taken off study gel (on study/off product). The medical care and referral of the participants who seroconvert will vary by site and will depend on both the local standard of care and the guidelines to be set by the National Institutes of Health.

## **8.9 Study Discontinuation**

This study may be discontinued at any time by NIAID, the HPTN, the product manufacturers, the US FDA, other government or regulatory authorities, or site IRB/ECs.

Monitoring of AEs/EAEs will be ongoing through regular SMC reviews (safety monitoring). If needed, the PSRT will convene ad hoc meetings in the event of an

abnormal number of reported AEs/EAEs judged definitely, probably, possibly, or probably not related to study gel or applicator, or any other conditions deemed as an emergency event by team members.

Decisions regarding discontinuation of study gel due to safety concerns are described in Section 6.2.

## **9 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT**

Each study site will adhere to standards of good laboratory practice, the HPTN CL Manual; and site-specific SOPs for proper collection, processing, labeling, transport, and storage of specimens to the LL. Specimen collection, testing, and storage at the LL will be documented using the HPTN Laboratory Data Management System (LDMS).

### **9.1 Local Laboratory Specimens**

As described in Section 5, the following types of specimens will be assayed at the LL:

- blood for CBC, LFT and RFP
- blood for HIV, HSV-2, and syphilis serology, and, HBsAg
- urine for pregnancy testing, GC and CT urine NAAT, and, dipstick urinalysis (microscopy and culture if indicated)
- vaginal smears for wet mount for BV, candidiasis, trichomoniasis and clue cells
- ecto-and endocervical cells for Pap smear

### **9.2 Central Laboratory Specimens**

As described in Section 5, the following types of specimens will be assayed at the HPTN CL:

- vaginal smears for Gram stain
- genital ulcer swab for multiplex PCR
- plasma for quality assurance HIV testing
- blood for plasma and serum archive (or LL if possible)
- HBV viral load testing
- cervical swab for cytokine and chemokine testing
- cervical swab for Gram stain
- vaginal swab for quantitative culture (US Site only)
- blood for PK analysis
- blood for storage for possible future HBV resistance testing

#### **9.2.1 Shipping to HPTN CL**

All specimens will be shipped in accordance with IATA specimen shipping regulations. All shipments will be documented using the HPTN LDMS.

### **9.3 Quality Control and Quality Assurance Procedures**

The HPTN CL has established a proficiency testing program at each study site. HPTN CL staff also will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control procedures, including proper maintenance of laboratory testing equipment, use of appropriate reagents, etc. HPTN CL staff will follow up directly with site staff to resolve any quality control or quality assurance problems identified through proficiency testing and/or on-site assessments.

Throughout the course of the study, the SDMC will select a random sample of stored specimens to test for quality assurance (QA) purposes. The total number of specimens undergoing QA testing will be about 50 samples or 10% of all specimens collected, whichever is greater.

The SDMC will inform site staff of the samples selected for the quality assurance testing, and site staff will ship the selected specimens to the HPTN CL. All specimens from participants who seroconvert will be collected. The HPTN CL will test the specimens for HIV antibody and compare the results of their tests with the results obtained by the local labs. The HPTN CL staff will follow up directly with site staff to resolve any quality assurance problems identified through the process.

### **9.4 Specimen Storage and Possible Future Research Testing**

Study staff will store serum and plasma collected from each study participant at the time of study entry, seroconversion (if applicable), and week 24 visit. All such specimens will be subject to possible safety and quality assurance testing during and after the study as described in Section 9.3 above, and will be destroyed at the end of the study after all protocol required and quality assurance testing has been conducted. In addition, CHBV participants will be asked to provide written informed consent for additional plasma specimens to be collected during the study and stored after the end of the study for possible future research testing. Any residual specimens of participants who do not consent to long-term storage and for future resistance testing will be destroyed at the end of the study, after all protocol required and quality assurance testing has been conducted.

### **9.5 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 currently recommended by the CDC. All infectious specimens will be transported in accordance with United States regulations (42 CFR 72).

## **10 ADMINISTRATIVE PROCEDURES**

### **10.1 Study activation**

Following ethical review and approval, study sites will submit required administrative documentation – as listed in the study-specific procedures manual – to the HPTN CORE. CORE staff will work with study site staff and complete DAIDS protocol registration in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual. Included in this step will be CORE and DAIDS review of each site-specific study informed consent form.

The DAIDS RCC Protocol Registration Office will review all site-specific informed consent forms and approve them for use according to DAIDS policies. The study cannot be initiated at a site until the site is fully registered with the DAIDS RCC Protocol registration office (through HPTN CORE) and has received written notification of protocol activation by CORE.

Pending successful registration and submission of all required documents, CORE staff will “activate” the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

### **10.2 Study Coordination**

DAIDS holds the IND application for this study (#55,690). Copies of all regulatory documents submitted to this IND by DAIDS will be forwarded to Gilead Sciences, Inc. for cross-referencing with the company’s other INDs for tenofovir gel. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS and Gilead Sciences, Inc.

Study site staff will be provided with the DAIDS SOPs for Source Documentation and Essential Documents; the Manual for Expedited Reporting of Adverse Events to DAIDS; and the DAIDS AE Grading Table. Training and written instructions outlining management and reporting, dispensing study gels and documenting product accountability, and other study operations will be provided.

Study case report forms will be developed by the study team and HPTN SDMC. Data will be transferred to the HPTN SDMC, entered, and cleaned using the SDMC DataFax data management system. Quality control reports and queries routinely will be generated and distributed to the study sites for verification and resolution.

Close coordination between the study site Investigator, NIAID Medical Officer, Protocol Specialist, Biostatistician, CORE Protocol Specialist, SDMC Protocol Operations Coordinator, Data Managers, and other protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow up, and AE incidence will be monitored closely by the team as well as the HPTN SMC. 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.

### **10.3 Study Monitoring**

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- verify compliance with human subjects and other research regulations and guidelines
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices
- confirm the quality and accuracy of information collected at the study site and entered into the study database

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures.

Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, HPTN CL, NIAID, Gilead Sciences, Inc., FDA, and US and in-country government and regulatory authorities. A site visit log will be maintained at the study site to document all visits.

### **10.4 Protocol Compliance**

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s)/EC(s) and the RCC prior to implementing the amendment.

### **10.5 Investigator's Records**

The Investigator will maintain, and store in a secure manner, complete, accurate and current study records throughout the study. In accordance with US regulations, the Investigator will retain all study records for at least two years following the date of marketing approval for the study gel for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. Study records include administrative documentation — including site registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

## **10.6 Use of Information and Publications**

Publication of the results of this study will be governed by DAIDS and HPTN policies. Any presentation, abstract, or manuscript will be submitted by the Investigator to the HPTN Manuscript Review Committee, DAIDS, and Gilead Sciences Inc., for review prior to submission.

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## **APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS**

## APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

EVALUATIONS	Screening (up to -56 days)	Final Screening	Enrollment Visit (Day 0)	Weeks 4, 12,	Weeks 8, 16, 20	Week 24 or Early Termination	Weeks 28, 32, 36 (CHBV participants )
Obtain informed consent (s)	X		X				
Obtain demographic information	X						
Obtain/update locator information	X	X	X	X	X	X	●
Obtain behavioral eligibility information	X						
Provide HIV/STI pre-test counseling	X	▲	X	▲	▲	X	
Provide HIV/STI risk reduction counseling	X	X	X	X	X	X	X
Provide HIV/STI post-test counseling	X	▲	X	▲	▲	X	▲
Obtain/update medical and menstrual history	X	X	X	X	X	X	●
Perform targeted physical exam	X						
PERFORM PELVIC EXAM:							
naked eye exam of external genitalia	X		X	X	▲	X	
speculum exam of vagina and cervix	X		X	X	▲	X	
colposcopic exam			X	X	▲	X	
vaginal pH - LL	X		X	X	▲	X	
wet mount for BV, candidiasis, trichomoniasis - LL	X		X	X	▲	X	
cervical swab for cytokine and chemokine testing - CL			X	X		X	
cervical swab for Gram stain - CL			X	X		X	
vaginal swab for quantitative culture (US site only) - CL			X	X		X	
vaginal swab for Gram stain assessment - CL	X		X	X		X	
genital ulcer swab for multiplex PCR - CL	▲		▲	▲	▲	▲	
ecto- and endocervical cells for Pap smear <sup>a</sup> - LL	X						
PERFORM LABORATORY EVALUATIONS:							
urine pregnancy test - LL	X	X	X	X	X	X	
urine NAAT for GC and CT - LL	X		X	▲	▲	X	
dipstick urinalysis-LL	X		X	▲	▲	X	
urine microscopy and culture - LL	▲		▲	▲	▲	▲	
HIV serology (EIA/WB when indicated) - LL	X	▲	X	▲	▲	X	
HBsAg - LL	X		X	▲	▲	X	
HBV viral load - CL			●	● <sup>b</sup>		●	●
PK sampling - LL				X	X <sup>c</sup>		
HBV serum archive (if participant provides consent) - LL			●	● <sup>b</sup>		●	●
syphilis serology - LL	X		X	▲	▲	X	
HSV-2 serology - LL	X		X	▲	▲	X	
plasma and serum archive - LL			X	▲	▲	X	
CBC - LL	X		X	X	▲	X	
LFT and RFP - LL	X		X	X	▲	X	● <sup>d</sup>

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## APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS continued

EVALUATIONS	Screening (up to – 56 days)	Final Screening	Final Screening/ Enrollment (Day 0)	Weeks 4, 12,	Weeks 8, 16, 20	Week 24 or Early Termination	Weeks 28, 32, 36 (CHBV participants)
Provide test results <sup>e</sup>	X	X	X	X	X	X	X
Offer/refer for STI treatment	▲	▲	▲	▲	▲	▲	
Obtain random assignment			X				
Provide study gel and instructions for use (with panty liners and/or menstrual pads, and condoms)			X	X	X		
Administer behavioral and adherence assessment			X <sup>f</sup>	X		X	
Administer acceptability assessment				X		X	
Administer study burden assessment						X <sup>g</sup>	● <sup>h</sup>

X - Protocol specific evaluation for all participants

▲ - If clinically indicated

● - CHBV participants only

a - Unless documentation of a normal Pap test result in the 90 days prior to screening

b - Assessment will be performed at Week 12 only

c - Assessment will be performed at Week 20 only

d - RFP only

e - When available

f - Behavioral assessment done only at the Enrollment Visit

g - Non-CHBV participants only

h - Assessment will be performed at Week 36 only

LL – at the Local Lab

CL – at the HPTN CL for assay





## **APPENDIX II: OUTCOMES, DIAGNOSTICS, AND FOLLOW UP EVALUATIONS**

## Appendix II: Outcomes, Diagnostics, and Follow up Evaluations

Condition	Gel Use	Evaluation	Follow up and Treatment Action
Deep Epithelial Disruption (Ulceration)	Hold study Gel (until evaluated)	Swab for herpes simplex culture. Perform syphilis serology (Herpes serology optional)	Re-evaluate in 48 - 72 hours and reinstate gel use if resolved. If the ulcer has become worse or not healed in 48 - 72 hours consider a biopsy. Ask participant to return in 7–10 days for follow up syphilis serology. If there is reoccurrence and there is no other aetiology, then consider permanent discontinuation.
Superficial Epithelial Disruption (Abrasion/Peeling)	Continue	Naked eye evaluation and/or colposcopy	Re-evaluate by speculum examination in 48 - 72 hours. If condition is significantly worse, hold gel use. Otherwise continue gel use.
Localized erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface	Continue	Naked eye evaluation and/or colposcopy	If asymptomatic, re-evaluate at next regularly scheduled visit. If symptomatic, re-evaluate by speculum examination in 5 - 7 days. If worsened significantly, hold gel use, until further evaluation is scheduled. Otherwise, continue gel use.
Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema	Hold study Gel (until evaluated)	Naked eye evaluation and/or colposcopy	Re-evaluate in 48 - 72 hours and reinstate gel use if resolved. If there is reoccurrence and there is no other aetiology, then consider permanent discontinuation.
Vaginitis	Hold study Gel (until evaluated, except for asymptomatic candida vaginitis)	Perform wet mount for candida vaginitis, trichomoniasis, and BV	Provide treatment and reevaluate in 48 - 72 hours. If resolved reinstate gel use.

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**APPENDIX II: OUTCOMES, DIAGNOSTICS, AND FOLLOW UP EVALUATIONS  
CONTINUED**

Condition	Gel Use	Evaluation	Follow up and Treatment Action
Intermenstrual Bleeding/Spotting	Hold study Gel (until evaluated)	Naked eye evaluation and/or colposcopy	If determined to be endometrial bleeding with no other source, continue gel use. Re-evaluate in 48 - 72 hours if the participant reports the bleeding/spotting has not resolved.
Suspected cervicitis (findings on exam such as discharge from the cervical os)	Continue (at clinician's discretion)	Evaluate for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> .	Re-evaluate in 48 - 72 hours. If condition is worse, hold gel use until further evaluation is scheduled
Petechial hemorrhage	Continue	Naked eye evaluation and/or colposcopy.	Re-evaluate by speculum examination in 48 - 72 hours. If condition is significantly worse, hold gel use, until further evaluation is scheduled. Otherwise continue gel use
Ecchymosis	Continue	Naked eye evaluation and/or colposcopy.	Re-evaluate by speculum examination in 48 - 72 hours. If the condition is significantly worse, hold gel use until further evaluation is scheduled. Otherwise continue gel use.
EAE that is judged by the site investigator or designee to be definitely, probably, possibly, or probably not related to the study gel or applicator	Hold study Gel (until evaluated)	Evaluate as according to current clinical practice at the site	Provide treatment as clinically indicated, when resolved reinstate gel use at clinician's discretion

- For trichomoniasis or symptomatic BV, treat or refer for treatment. If resolved, restart gel use. If observed at Week 24 visit, treat and follow up to document resolution
- For symptomatic candida vaginitis: manage with oral medication and re-evaluate in 3 - 5 days. If resolved, restart gel use. If observed at Week 24 visit, treat and follow up to document resolution
- For asymptomatic candida vaginitis:
  - o If a participant has asymptomatic candida vaginitis she should continue gel use and be re-evaluated in 7 days
  - o If at the Week 24 Visit there are signs and symptoms compatible with vaginitis, treat and follow up to document resolution

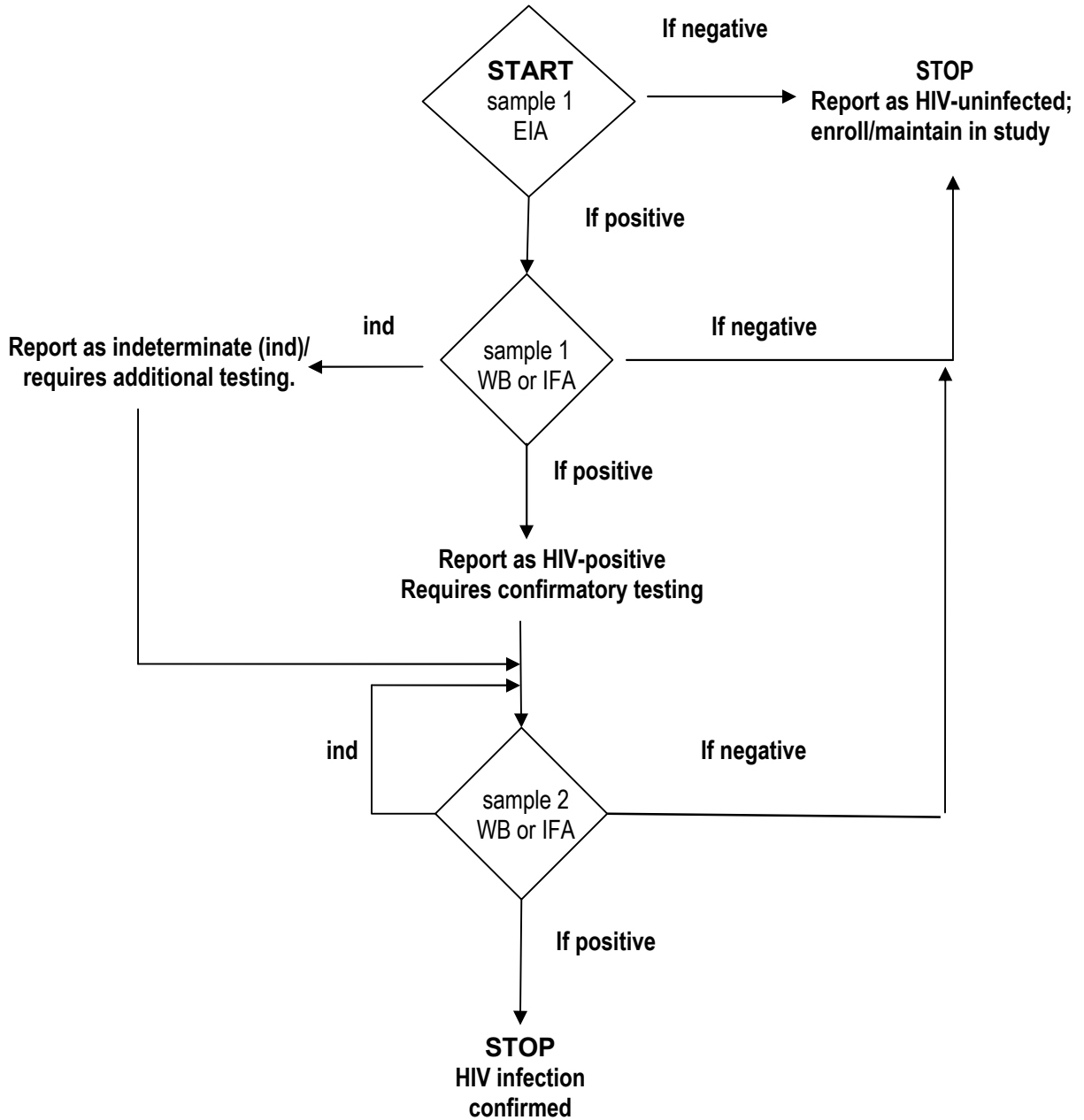


## **APPENDIX III: HPTN HIV ANTIBODY ALGORITHM**

# APPENDIX III:

## HPTN HIV Antibody Testing Algorithm

### NON-RAPID TESTING



**APPENDIX IV: SAMPLE INFORMED CONSENT FORMS**



**DIVISION OF AIDS  
HIV Prevention Trials Network (HPTN)  
SAMPLE SCREENING INFORMED CONSENT FORM**

**HPTN 059  
Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1%  
Tenofovir Gel**

**Final Version  
Version 1.0  
17 March 2005**

**PRINCIPAL INVESTIGATOR: [insert]  
PHONE: [insert]**

**Short Title for the Study:**

HPTN 059 Safety and Acceptability Study of 1% Tenofovir Gel

**Introduction**

You are being asked to take part in these screening exams and tests because you are a sexually active woman between the ages of 18 and 50, and you may be able to join the research study named above. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. The screening exams and tests include interview questions, urine and blood tests, a physical exam, and an exam of your vagina.

This is a consent form. It gives you information about the screening exams and tests. The study staff will explain the exams and tests to you and what is expected of you. You are free to ask questions about the screening exams and tests at any time. If you agree to have the screening exams and tests, you will be asked to sign this consent form or make your mark in front of a witness. You will be offered a copy to keep.

**Why Are These Screening Exams and tests Being Done?**

The main purpose of these screening exams and tests is to find out if you can join a research study. The research study will try to find out if there are any bad effects when women apply tenofovir gel in the vagina for 24 weeks. About half of the women in the research study will insert the gel into the vagina at bedtime every day. The other half of the women will insert the gel into the vagina before having sex. The other purpose of the study is to find out what women think about the gel.

Although tenofovir pills have been approved by the US Food and Drug Administration (FDA) for HIV treatment, the gel is “experimental”. This means we do not know all the effects it may have. We do not know if it works to stop HIV from getting into the body. This is one of the reasons the study is being done. Because the gel is experimental, the FDA and [LOCAL AUTHORITY] [HAS/HAVE] not approved it for use in the general community. The FDA has been informed of this study and has allowed it to happen. The [local authority] has also allowed the study to happen.

Before a large study can be done to find out if tenofovir gel stops HIV from getting into the body, we must first make sure it is safe. So far, the safety of the gel has been tested among 84 women in the United States. They applied the gel in the vagina every day for two weeks. In that study, the gel was shown to be safe and women in the study did not have a lot of complaints or problems. The most common complaints were dryness, itching, burning, or pain in the genital area. Some women also complained that the gel leaked out of the vagina.

The United States National Institutes of Health is providing funds for this study to take place. About 200 women from New York, USA and, Pune, India, will join this study (100 women at each site). About 100 women will be in the study here at – [INSERT NAME OF SITE]. The whole study will take about one and half years to finish. Each woman will be in the study for about eight to twelve months. It will take about one week to two months to complete the screening exams and tests. It will take about six to nine months to complete the main study exams and tests. If you can join the study, you will be asked to use the study gel for six months. You will have a study visit every month for those six months. If you have chronic hepatitis B liver infection, after you have stopped using the study gel, you will be asked to return to the clinic for another three months. You will have a study visit every month for those three months for a blood test.

Some people may not be able to join the study because of information found during the screening exams and tests.

### **What Do I Have To Do If I Take Part in the Screening Exams and tests?**

If you agree to have the screening exams and tests, you will have one or two screening visits here at the study site. The exams and test will take about one week to two months. Depending on what your screening exams and tests show, more screening visits may be needed. All screening exams and tests will be done within two months. If all exams and tests are not done within two months, and you still want to find out if you can join the research study, you will have to start the screening exams and tests over from the beginning.

Your first visit will continue today, after you read, discuss, and, sign or make your mark on this form. No study exams or tests will be started before the screening exams and tests have been fully explained to you and you have signed this form.

The visit will take about one to two hours.

To find out if you can join the study you will be asked some questions. The questions will be about you and where you live. You will be asked questions about your health, the medicine you take, your periods, and how you have sex. Some people may be embarrassed by questions about how they have sex.

If your answers to the questions show that you may join the study, you will have to give urine for a pregnancy test. You will receive the result of your pregnancy test today. If you are pregnant, you will not be able to join the study. However, site staff will talk to you about options available to you. They will refer you to available sources of medical care and other services you may need. If the study is still open after your pregnancy, you can come back here to find out if you can join the study then.

If you are not pregnant, study staff will talk to you about HIV and other sexually transmitted infections (STIs). You will have tests for HIV, gonorrhea, chlamydia, hepatitis B virus, syphilis, bacterial vaginosis, candidiasis, trichomonas, and herpes simplex virus. You will talk about HIV/AIDS and other STIs. You will also talk about ways that HIV and other STIs are spread, and ways to protect against them. You will talk about what it may mean to know the results of these tests. You can discuss whether you are prepared to receive the test results. If you are having health problems that may be due to STIs, the study staff will refer you for treatment or give you medicine to treat them.

It is not known if the study gel will work to protect against pregnancy, therefore you should not use the study gel as a birth control method. You must agree to use an effective method of birth control such as birth control pills or another hormonal based method (except for vaginal rings), an intrauterine device (or IUD), be sterilized, or have sex with a partner who is sterilized.

The study staff will provide condoms to you free of charge.

If you are willing to have HIV and STI testing, you will give blood (about 30 mL or two tablespoonfuls) [LOCAL EQUIVALENT - SITES TO COMPLETE] and urine for the tests. You must know what your HIV test says to join the study.

Your urine will also be tested for infections. Your blood will be tested for HIV. Your blood will also be tested to check on your general health, and the health of your liver, kidneys and blood. It takes about [X AMOUNT OF TIME - SITES TO COMPLETE] before your results are ready. We will give you your results as soon as they are ready.

You will have a physical exam and a pelvic exam. During the pelvic exam the study doctor or nurse will use a speculum. A speculum is a plastic or metal instrument used to separate the walls of the vagina. It is used so that the study doctor or nurse can examine the vagina and the cervix during the exam. The part of the speculum that is inserted into the vagina looks a little like two spoons hinged together. With the speculum inside the vagina, the study doctor or nurse gently pushes the walls of the vagina apart

by spreading the “spoons” away from each other.

Using the speculum makes it easier for the doctor or nurse to check the vagina and cervix. They will check for discharge, or other signs of infection, and other possible problems. The study doctor or nurse will also take some fluids to test for STIs and other possible problems.

If a sore (or other problem) is seen during the exam of your vagina, you may need medicine to treat it. You will be asked to see your regular health care provider for medicine or be given medicine here. We will ask you to come back here after a few days for another exam. If the sore (or other problem) has cleared up when you come back, you may be able to join the research study.

The study staff also will collect samples from your cervix to test for anything that is not normal. If the test is not normal, it could mean you have cervical cancer, or that it could lead to cervical cancer. This test is called a “Pap test”. It takes about [X AMOUNT OF TIME – SITES TO INSERT] before Pap test results are ready. We will give you the results as soon as they are ready. The results of your Pap test may affect whether you can use the gel being tested in the research study.

It takes about [X AMOUNT OF TIME – SITES TO INSERT] before HIV and STI test results are ready. We will give you the results for all your exams and tests as soon as they are ready. You will talk with the study staff about the meaning of your test results and how you feel about them.

If your tests show that you have HIV you will not be able to join the study. The study staff will refer you to available sources of medical care and other services you may need for HIV. They will tell you about other studies that you may be able to join.

If your exams and tests show that you have an STI, you may need medicine to treat it. The study staff will refer you to your usual health care provider for medicine or give you medicine here to treat the STI. You will be asked to come back here after taking all the medicine. At that time, you will be able to enter the research study.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE:]

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

If your exams and tests show no problems, you will be able to enter the research study. You will receive a different Informed Consent Form if you return for the Enrollment Visit.

If at any time during the screening it is found that you cannot join the study, the screening process and your visit will end.

### **Why Would The Doctor Stop the Screening Procedures Early?**

The study doctor may need to stop the screening exams and tests early without your permission if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), U.S. National Institutes of Health (NIH), the drug company supporting this study, the Ethics Committees, the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.)
- Your exams, tests and answers to the questions show you can not join the study.
- The study staff feels that having the screening exams and tests would be harmful to you.
- You do not want to find out your HIV test result.
- You are not able to come to the visits or complete the screening exams and tests.
- Other reasons that may prevent you from completing the study.

### **What Are The Risks Of The Study?**

#### Risk of Blood Draws:

You may feel discomfort or pain when your blood is drawn. You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

#### Risk of Genital Exams:

You may feel discomfort or pressure during the exam of your genital area and inside your vagina. You may have mild vaginal spotting (bleeding). The mild bleeding will stop shortly after the exam.

#### Other Possible Risks:

You may become embarrassed, worried, or nervous when discussing how you have sex, ways to protect against HIV and other infections passed during sex, and your test results. You may become worried or nervous while waiting for your test results. If you have HIV or other infections, knowing this could make you worried or nervous. A trained counselor will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy while you are having the screening exams and tests. Your visits here will take place in private. However, it is possible that others may learn that you are taking part in the study here. Because of this, they may treat you unfairly. For example, you could have problems getting or keeping a job, or being accepted by your family or community.

### **Are There Benefits To Taking Part In This Study?**

You may get no direct benefit from the screening exams and tests. However, you will have a physical exam and a pelvic exam, and counseling and testing for HIV and STIs. You will also have tests to check your general health and the health of your liver, kidneys, and blood. This study can not provide you with medical care, but study staff will refer you to other available sources of care.

If your Pap test result is not normal, you will be referred for treatment at the [INSERT NAME OF PROVIDER/CENTER].

You will get counseling and testing for HIV. You will get free condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your own health care provider. You will get counseling and testing for other infections. If you have these infections, you will be referred for treatment or get medicine to treat them here, if needed. You can bring your partner here for tests and treatment or referral for treatment for these infections if he needs them.

### **What Other Choices Do I Have Besides This Study?**

You do not have to participate in this study, if you choose not to.

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

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

Please talk to your doctor about these and other choices that may be available to you.

### **What About Confidentiality?**

Efforts will be made to keep your personal information private. We cannot guarantee absolute confidentiality. Your personal information may be released if required by law. If this study is published, your name will not be used and you will not be personally identified.

Your records may be reviewed by:

- The U.S. Food and Drug Administration (FDA)
- U.S. National Institutes of Health (NIH)
- The local government or regulatory agency
- [INSERT NAME OF SITE] IRB
- Study staff
- Study monitors
- Ethics committees
- Drug companies supporting this study

[FOR US SITE INSERT: The study staff will do everything they can to keep your personal information private, and they will have a Certificate of Confidentiality from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your taking part in the study. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staffs learn of possible child abuse and/or neglect or a risk of harm to yourself or others, they will have to tell the proper authorities.]

### **What Are The Costs To Me?**

There is no cost to you for the screening exams and tests.

### **Will I Receive Any Payment?**

You will be paid for your time and effort for each screening visit. You will receive [INSERT SITE - SPECIFIC AMOUNT OF MONEY] visits. You will also be paid for other costs to you for coming to the screening visits [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE]. There may be one or more screening visits.

### **What Happens If I Am Injured?**

It is unlikely that you will be injured as a result of having the screening exams and tests. If you are injured as a result of having the screening exams and tests, you will be given immediate treatment for your injuries. However, you may have to pay for this care. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

[SITES TO SPECIFY INSTITUTIONAL POLICY]

### **What Are My Rights As A Research Subject?**

Taking part in the screening exams and tests is completely voluntary. You may choose to not have the screening exams and tests any time. You will be treated the same no matter what you decide. If you choose to not have the screening exams and tests, you will not lose the benefit of services to which you would normally have at this clinic.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

### **What Do I Do If I have Problems or Questions?**

For questions about the screening exams and tests or if you have a research-related injury, you should contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research subject, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]



**SIGNATURE PAGE**

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB/EC]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to take part in this study, please sign your name or make your mark below.

\_\_\_\_\_  
Participant's Name (print)

\_\_\_\_\_  
Participant's Signature and Date

\_\_\_\_\_  
Study staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study staff Signature and Date

\_\_\_\_\_  
Witness' Name (print)  
(As appropriate)

\_\_\_\_\_  
Witness's Signature and Date

**DIVISION OF AIDS  
HIV Prevention Trials Network (HPTN)  
SAMPLE ENROLLMENT INFORMED CONSENT FORM  
HPTN 059**

**Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1%  
Tenofovir Gel**

**Final Version  
Version 1.0  
17 March 2005**

**PRINCIPAL INVESTIGATOR: [insert]  
PHONE: [insert]**

**Short Title for the Study:**

HPTN 059 Safety and Acceptability Study of 1% Tenofovir Gel

**Introduction**

You are being asked to take part in this research study because you are a sexually active woman between the ages of 18 and 50. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to join this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form or make your mark in front of a witness. You will be offered a copy to keep.

**Why Is This Study Being Done?**

The main purpose of the study is to see if there are any bad effects when women use tenofovir gel in the vagina for 24 weeks. About half of the women in the research study will insert the gel into the vagina at bedtime every day; the other half of the women will insert the gel into the vagina before sex. The other purpose of the study is to find out what women think about the gel.

Although tenofovir pills have been approved by the FDA for HIV treatment, the gel is “experimental”. This means we do not know all the effects it may have. We do not know if it works to stop HIV from getting into the body. This is one of the reasons the study is being done. Because the gel is experimental, the FDA and [LOCAL AUTHORITY] [HAS/HAVE] not approved it for use in the general community. The FDA has been informed of this study and has allowed it to happen. The [LOCAL AUTHORITY] has also allowed the study to happen.

Before a large study can be done to find out if tenofovir gel protects against HIV, we must first make sure that it is safe. So far, the safety of the gel has been tested among 84 women in the United States who applied the gel in the vagina every day for two weeks. In that study, the gel was shown to be safe and women tested did not have a lot of complaints or problems with the gel. The most common complaints were dryness, itching, burning, or pain in the genital area. Some women also complained that the gel leaked out of the vagina.

It is not known if tenofovir gel will protect you from becoming infected with HIV. Therefore, you should not do anything that might expose you to HIV (such as unprotected sex or sharing needles for injection).

The United States National Institutes of Health is providing funds for this study to occur. About 200 women from New York, USA and, Pune, India, will take part in this study (100 women at each site). About 100 women will be in the study here at – [INSERT NAME OF SITE]. The whole study will take about one and half years to finish. Each woman will be in the study for about eight to twelve months. It will take about one week to two months to complete the screening exams and tests. If you can join the study, you will be asked to use the study gel for six months. If you have chronic hepatitis B, you will be asked to return to the clinic each month for three more months after you’ve stopped using the study gel for blood tests.

### **What Do I Have To Do If I Am In This Study?**

If you decide to join this study, and your tests and answers to the questions show you can join, you will be placed in one of four study groups. Two groups will get tenofovir gel. Out of the two groups that get tenofovir gel, one group will apply the gel once daily, and the other group will apply the gel before sex. If you use the gel with sex you will not use it more than twice a day. The other two groups will get a placebo gel. The placebo gel is a gel that looks and feels like tenofovir gel, and it is made up of all the same ingredients except tenofovir (the active ingredient). Out of the two groups that get the placebo gel, one group will use the gel once daily, and the other group will use the gel before sex but not more than twice a day. The study group will be chosen by chance, like flipping a coin, or throwing dice [SITE TO MODIFY TO LOCAL EQUIVALENT]. You cannot choose your group, and the study staff cannot choose your group for you. You have an equal chance of being placed in any one of the groups. Neither you nor the study staff will know whether you are in the placebo or tenofovir groups.

**All four groups are important to this study. No matter which study group you are in, you must remember that we do not know if any of the study gels work to protect women from getting HIV. The only known way to protect against getting HIV during sex is to use a condom every time you have sex.**

**It is not known if the study gel will work to protect against pregnancy, therefore you should not use the study gel as a birth control method. You must agree to use effective method of birth control such as birth control pills or another hormonal based method (except for vaginal rings), an intrauterine device (or IUD), be sterilized, or have sex with a partner who is sterilized.**

The study staff will provide condoms to you free of charge.

Each visit is described below. Your visits will not occur while you are having your period. You will insert into the vagina one applicatorful, about four grams (about one teaspoonful), of the gel. One group of women will use the gel at bedtime every day. The other group will use the gel up to two hours before each act of vaginal sex, but not more than twice a day. You will use the gel for 24 weeks. Once you join the study, you will return to the site for a follow up visit every four weeks for six visits.

After your six monthly visits, you will stop using the study gel. In total, you will have seven study visits including today's visit.

If you have chronic hepatitis B, you will have the six monthly visits and an additional three visits. The additional three visits will occur every month after you have stopped using the gel, for three months, for a total of ten study visits including today's visit.

After all the participants finish the study, and we find out the results of the study, if you wish, you will be told which gel you received.

### **Final Screening/Enrollment Visit:**

If you decide to take part in this study, your first visit will continue today, after you read, discuss and sign or make your mark on this form. No study procedures will be started before the visit exams and tests have been fully explained to you and you have signed this form. It will take about one hour.

To find out if you still can join the study you will be asked some questions - the questions will be about you, where you live, and other questions about your health, your periods, the medicine you take, and your sexual practices. Some people may be embarrassed by questions about their sexual history. Many of these questions and blood and urine tests are the same as the ones at the Screening Visit.

If your answers to the questions show that you can join the study, you will:

- Give urine for a pregnancy test. You will be given your result for the pregnancy test today. If you are pregnant, you will not be able to join the study; however site staff will talk to you on options available to you, and will refer you to available sources of medical care and other services you may need. If the study is still open after your pregnancy, you can come back here to find out if you can join the study then.
- You will have a pelvic exam. The study doctor or nurse will use a speculum. A speculum is a plastic or metal instrument used to separate the walls of the vagina so that the study doctor or nurse can examine the vagina and the cervix. The part of the speculum that is inserted into the vagina looks a little like two spoons hinged together. With the speculum inside the vagina, the study doctor or nurse gently pushes the walls of the vagina apart by spreading the “spoons” away from each other. The doctor or nurse will check the vagina and cervix for discharge, or other signs of infection, and other possible problems. During the pelvic exam, the study doctor or nurse will look at your genital area and into your vagina through a lens called a colposcope. The lens works like a magnifying glass to help the nurse or doctor see anything that may not be normal. The lens will not be inside your body. They may take photos with a camera. The study doctor or nurse will also take some fluids to test for STIs and other possible problems.

If a sore (or other problem) is seen during the exam of your vagina, you may need medicine to treat it. You will be asked to see your regular health care provider for medicine or be given medicine here. We will ask you to come back here after a few days for another exam. If the sore (or other problem) has cleared up when you come back, you may be able to join the research study.

If your exams and tests show no problems today, you will be able to join the study. You will find out if you are in the group that uses the study gel once daily or the group that uses the study gel before sex, but not more than twice a day.

To make sure it is safe for you to use the gel, you will give blood (about 30 mL or two tablespoonfuls) [OR LOCAL EQUIVALENT - SITES TO INSERT] and urine for the following tests:

- An HIV test. You must receive your HIV test results again to remain in the study.
- A hepatitis B test
- STI testing and counseling
- Urine test for infections
- Blood tests to check the overall health of your blood cells, and the health of your liver and kidneys.

It takes about [X AMOUNT OF TIME – SITES TO INSERT] before HIV and STI tests and blood test results are ready. We will give you the results from all the exams and tests as soon as they are ready. You will talk with the study staff about the meaning of your test results and how you feel about them.

If your exams and tests show that you have an STI, the study staff will refer you to your regular health care provider. They may give you medicine here to treat the infections. You will be asked to come back here after taking all the medicine for a check-up. After the STI has been treated, you may then be able to join the study.

After the study staff determine that you qualify for the study, at your enrollment visit and your last visit, some of your blood will be frozen and kept at the clinic while you are in the study. If needed, they will test this blood later in the study to help check on your health. Your blood also may be sent to Johns Hopkins University in the United States. Johns Hopkins University will test your blood for HIV and compare their results with our results. This will make sure that the HIV test result is correct.

If you have hepatitis B you will:

- Give extra blood (about 5 mL or 1 teaspoonful) [OR LOCAL EQUIVALENT – SITE TO INSERT] to check the viral levels of the hepatitis infection. The study staff will give you the results of your tests [IN X AMOUNT OF TIME – SITES TO INSERT].
- If you agree, give extra blood (about another 5 mL or 1 teaspoonful) [OR LOCAL EQUIVALENT – SITE TO INSERT] for storage for future testing to see how the hepatitis virus responds to tenofovir. You will receive a different Informed Consent Form if you agree to give extra blood for future testing.

You will be given tubes of either tenofovir gel or placebo gel with applicators. You will also be given instructions on how to use them. You will receive condoms, and panty liners and/or menstrual pads.

In addition to your study visits, you will be asked to do the following:

- Use an effective method of contraception during the study.
- Contact the study doctor or nurse if you have any discomfort or medical problems.
- Tell the study staff about any medications you take while in the study.
- Agree to use study provided panty liners and/or menstrual pads for your period, or in case the study gel leaks out of the vagina. If you need a different kind other than the kind provided to you by the study, let the study staff know. You can use your own tampons during your period.
- Be willing to use the condoms the study staff will give you. You **must not** use spermicides or condoms lubricated with spermicides, during the study. If you need to use a different kind other than the ones provided to you by the study, let the study staff know.

You **must not** do the following during the entire time while in the study:

- Use intravenous drugs except for medical use.
- Take part in studies of other vaginal products or any drug or device study. Tell the study staff if you plan to join another study.
- Use other participants' study gel.
- Douche or otherwise clean the vagina, or insert other products into your vagina, two hours before and two hours after having sex.

### **Follow Up Visits:**

Each monthly visit will take about an hour. The visits will not be scheduled during your period. You will have the following routine procedures at your six monthly visits:

- Tell the study staff any updated information about your address, telephone number or other contact information.
- Tell the study staff if you had any medical problems or discomfort since your last visit.
- Talk to study staff about ways to prevent HIV and STIs.
- Tell the study staff any new information about your health or your periods.
- Tell the study staff about any medicines you are taking.
- Give urine for a pregnancy test. You will receive the results of your pregnancy test day of the visit.
- Will be provided with the study gel and pantyliners and/or menstrual pads, and, condoms with instructions on how to insert the gel (except Month 6 visit).

### **Visits 1 and 3 (Months 1 and 3):**

You will complete all of the regular monthly procedures plus:

- Answer questions about your use of the gel.
- Tell the study staff your thoughts and opinions about the gel.
- Have a pelvic exam with a speculum, and with a colposcopic lens.
- Give blood about 10 mL or two teaspoonsful) [OR LOCAL EQUIVALENT – SITE TO INSERT]. We will check your blood for the overall health of your blood cells, and the health of your liver and kidneys, the study staff will give you the results of your tests [IN X AMOUNT OF TIME – SITES TO INSERT]. Your blood will also be checked to see if any of the gel gets into your blood.

If you have hepatitis B at Visit 3 (Month 3) you will:

- Give extra blood (about 5 mL or 1 teaspoonful) [OR LOCAL EQUIVALENT – SITE TO INSERT] to check the viral levels of the hepatitis infection. The study staff will give you the results of your tests [IN X AMOUNT OF TIME – SITES TO INSERT].
- If you agree, give extra blood (about another 5 mL or 1 teaspoonful) [OR LOCAL EQUIVALENT – SITE TO INSERT] for storage for future testing to see how the hepatitis virus responds to tenofovir. You will receive a different Informed Consent Form if you agree to give extra blood for future testing.

### **Visits 2, 4, and 5 (Months 2, 4, and 5)**

You will:

- Have all the routine procedures.
- At the month 5 Visit, give blood (about 5 mL or 1 teaspoonful) [OR LOCAL EQUIVALENT – SITE TO INSERT] to check if any of the study gel has been absorbed into your blood.

At Visit 5 (Month 5) you will do the following procedure in addition to those mentioned above:

- Give blood to check if any of the gel has been absorbed into your blood

### **Visit 6 (Month 6)**

You will stop applying the study gel at this visit. You will complete all of the routine monthly procedures plus:

- Answer questions about your use of the gel.
- Answer some questions about how you used the gel, and your thoughts and opinions of the gel.
- Have an HIV test.
- Have a hepatitis B test.
- Have STI tests.
- Have counseling about HIV and other STIs before your tests, and after your tests if needed.
- Talk about ways that HIV and other STIs are spread, and ways to protect against them.
- Have a pelvic exam with a speculum, and with a colposcopic lens.
- Give blood (about 30 mL or 2 tablespoonsful) [OR LOCAL EQUIVALENT – SITE TO INSERT] and urine for STI tests and infections
- Your blood will be checked for the overall health of your blood cells, and the health of you liver and kidneys



If you do not have hepatitis B at this visit you will:

- Answer some questions about your thoughts and opinions about the study and how easy or difficult it was to be in the study.

If you have hepatitis B you will:

- Give extra blood (about 5 mL or 1 teaspoonful) [OR LOCAL EQUIVALENT – SITE TO INSERT] to check the viral levels of the hepatitis infection.
- If you agree, give extra blood (about 5 mL or 1 teaspoonful) [OR LOCAL EQUIVALENT – SITE TO INSERT] for storage for future testing to see how the hepatitis virus responds to tenofovir.

The study site staff will give you your test results as soon as they are available. The results may be given to you by phone. If you give your permission, the study site staff can visit you at your home or a place in your community. If your HIV test results are positive, they will not be given to you over the phone. We will ask you to come back to the clinic or will visit you at your home or a place in your community.

### **After You Finish Using the Gel:**

During this study you may have a chance to take part in additional studies. If you choose not to take part in any of our additional studies, your participation in this study remains the same.

If you have any problems or concerns regarding your health after using the gel, let the study staff know. You can contact the study site staff at any time after you have finished using the gel. The study site staff may want to let the study sponsor about any serious problems you tell them about.

If you have hepatitis B:

### **Visits 7, 8 and 9 (Months 7, 8 and 9):**

You will return to the site for an additional three visits and will:

- Tell the study staff information about your address, telephone number or other contact information.
- Tell the study staff if you had any medical problems or discomfort since your last visit.
- Talk to study staff about ways to prevent HIV and STIs.
- Tell the study staff about your health or your periods.
- Tell the study staff about any medicines you are taking.

- Give blood (about 5 mL or 1 teaspoonful) [OR LOCAL EQUIVALENT – SITE TO INSERT] to check your liver, and your hepatitis B virus levels to see if the hepatitis gets worse. The study staff will give you the results of your tests [IN X AMOUNT OF TIME – SITES TO INSERT].
- If you agree, give extra blood for storage for future testing. (about another 5 mL or 1 teaspoonful) [OR LOCAL EQUIVALENT – SITE TO INSERT]
- At month 9 only, answer some questions about your thoughts and opinions about the study and how easy or difficult it was to be in the study.

### **Any Time During The Study:**

If the study staff think you may have become pregnant, you will give urine for a pregnancy test. Also, if you are having health problems that may be caused by infections passed during sex, you will:

- Have an exam of your genital area and inside your vagina.
- Give blood or urine to test for infections passed during sex.
- Get treatment for infections passed during sex if you need it.

You are asked to tell the study staff about any medical problems you have, especially genital problems. You can contact the study staff between regular visits to report these problems. The study staff will examine you as necessary. They will either provide or refer you for medical care that you may need.

If the staff find that a study gel is causing you problems, they may ask you to stop using the gel, either for a short time or permanently. The study staff will ask you to stop using the gel if you become pregnant or if you become infected with HIV. Even if you stop using the gel, you will be asked to stay in the study and have your follow up visits. You will have some or all of the originally planned exams and tests that the study staff would like you to have to check on your health.

If you have an infection passed during sex that your partner also may have, you can bring him here for counseling and referral for treatment.

You can have extra counseling and testing for HIV if needed between regular visits. If you wish, your partner can have counseling with you. If you become infected with HIV, you can stay in the study but you cannot keep using the gel.

The study staff will give you counseling and refer you to available sources of medical care and other services you may need.

At each study visit, the study staff will update information on where you live and how to keep in contact with you. They will use this information to remind you of scheduled visits. If you miss a visit, the study staff will try to contact you by [SITE-SPECIFIC METHODS]. If you give your permission, they also may visit your home to find you. They

will try to reach you through the contact people that you list. If they talk to these people, they will not tell them why they are trying to reach you.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE:]

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

### **How Many Women Will Take Part In this Study?**

About 200 women will take part in this study. About 100 women will be from New York. About 100 women will be from India.

### **How Long Will I be In This Study?**

You will be in this study about six to eight months. You will be asked to apply the study gel for 24 weeks. The total time you will be on the study, including the time to complete the screening exams and tests and the main study is eight to twelve months.

### **Why Would The Doctor Take Me Off This Study Early?**

The study doctor may need to take you off the study early without your permission if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), U.S. National Institutes of Health (NIH), the drug companies supporting this study, the Ethics Committee, the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.)
- Data and Safety Monitoring Board (DSMB) recommends that the study be stopped early (A DSMB is an outside group of experts who monitor the study)
- You are not able to come to the study visits or follow the procedures required by the study.
- You do not want to find out your HIV test result.
- You are not able to keep appointments or apply gel as instructed.
- Other reasons that may prevent you from completing the study successfully.

The study doctor will ask you to stop using the gel but continue to come in for your follow up visits and procedures if:

- You are pregnant.
- You become infected with HIV.

- The study doctor decides that continuing in the study would be harmful to you or your partner.
- You need a treatment that you may not take while on this study.
- You have a bad reaction to the gel.

You will stop using the study gel until the study doctor decides it is safe for you to start using the gel again, if possible.

### **What are the risks of this study?**

#### **Risks of Blood Draws:**

When your blood is taken, you also may feel discomfort .You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

#### **Risk of Genital Exams:**

You may feel discomfort or pressure during the exam of your genital area and inside your vagina. You may have mild vaginal spotting (bleeding). The mild bleeding will stop shortly after the exam.

#### **Other Possible Risks:**

You may become embarrassed, worried, or nervous when discussing sexual behaviors and HIV. You may become worried or nervous while waiting for your STI and HIV test results. If you have HIV, knowing your HIV status could make you worried or nervous. You will talk with a trained staff member who will help you deal with any feelings or questions you have.

#### **Risks of Tenofovir Gel:**

It is very important to use the study gel as instructed by staff. The gel used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study drug side effects please ask the study staff at your site.

Some of the effects of the tenofovir gel are still unknown. Some possible effects are dryness, itching, burning, or pain in the genital area. You may also have discharge if the gel comes out of the vagina. The study staff will give you panty liners and/or menstrual pads in case you need them. In about half of the women tested before, there was a small amount of irritation in the genital area.

It is possible that tenofovir gel could be absorbed from the vagina into the blood. Based on the earlier study of tenofovir gel, a small amount (about 1% of the amount that is absorbed when the oral pill is taken) of tenofovir gel from the vagina was absorbed into

the blood in about half of the women tested. If the gel is absorbed into the blood, it is not known whether this will cause any bad effects.

There are other side effects in patients taking the oral form (a pill) of tenofovir which is absorbed into the blood. However, these side effects may have been because of other medicines that patients were taking or because of the HIV itself. We are still learning about the gel, and some side effects may not be known.

The following side effects have been associated with the use of tenofovir pills:

- Upset stomach, vomiting, gas, loose or watery stools.
- Dizziness.
- Abdominal pain.
- Lack of energy.
- Kidney damage or failure.
- Inflammation or swelling and possible damage to the pancreas.
- Shortness of breath.
- Rash.
- Low phosphate, a chemical in the blood.
- Allergic reaction, which may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath or a general feeling of illness.
- Changes in bone growth and strength were seen in study animals given tenofovir. It is unknown if taking tenofovir for a long time will cause bone abnormalities in adults. In children, some decrease in bone thickness (density) has been seen.

It is not known what effect tenofovir gel could have on the HIV virus. There is a small possibility that tenofovir could change the virus. If the virus changes normal treatment for HIV may not work on the virus. If you or your partner should become HIV positive during the study you should stop using the study gel immediately.

It is not known what effect tenofovir gel could have on the hepatitis B virus. There may be a risk that tenofovir will change the hepatitis B virus. If the virus changes normal treatment for hepatitis B may not work on the virus. It is not known what effect tenofovir gel could have on the disease condition in people with hepatitis B virus. It is possible that if you have hepatitis B virus, it may become worse when you stop applying the gel.

#### Possible Risks to Your Privacy

We will make every effort to protect your privacy while you are in this study. However, it is possible that you could have problems if people learn that you are in this study and think that you are infected with HIV or at risk of HIV because of sexual behavior or illegal drug use, or at high risk for HIV. Because of this, others may treat you unfairly. For example, you could have problems getting or keeping a job. You also could have

problems being accepted by your family or community. There also is a risk to your privacy someone else in taking part in this study knows you.

### **Are There Risks Related To Pregnancy?**

Because there is only a small amount of information on tenofovir in pregnant women, tenofovir should be used during pregnancy only if clearly needed. You must agree to try to not become pregnant during the study.

It is not known if the gel used in this study harms unborn babies. You and your partner must be willing to use an effective method of birth control such as birth control pills or another hormonal based methods (except for vaginal rings), an intrauterine device or IUD, be sterilized, or have sex with a partner who is sterilized. You should discuss this with the study staff. You must be willing to continue to use birth control for one month after you stop applying the gel.

The study staff will provide condoms to you free of charge.

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant.

### **What If I Have A Positive Pregnancy Test During The Study?**

If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices. If you have a positive pregnancy test while using the study gel, we will ask you to stop using the study gel, but will ask you to continue to be in the study and to come in for your follow up visits. There are no anticipated additional risks to you if you choose to continue to take part in this study.

We will ask you to return for another pregnancy test in six weeks (in addition to your next regularly scheduled visit). If your pregnancy test in six weeks is negative, you can start using the gel again.

If you are pregnant, this study will not provide care related to your pregnancy, the delivery of your baby, or the care of the baby. Your baby may have been exposed to tenofovir if the gel was absorbed from the vagina into your blood, and we do not know if this will affect unborn babies. The study staff will contact you to ask you a few questions about the outcome of your pregnancy. You must arrange for your care and your baby's care outside of this study. The study staff will talk with you about care for your baby once he or she is born.

## Breastfeeding

It is unknown if there are any effects of tenofovir gel on breast-milk. It is unlikely that the gel will pass through breast milk but absorbing the gel from the vagina into the blood may affect breast milk and may cause harm to your infant. You must agree to not breastfeed during this study.

## Are There Benefits To Taking Part In This Study?

If you take part in this study, there may be no direct benefit to you because no one knows if the study gel will prevent HIV infection. Also, you may be in the study group that receives the placebo gel, which will not help in preventing HIV. Information learned from this study may help in the development of ways to prevent the spread of HIV in the future.

You will receive pelvic exams and counseling and testing for HIV and STIs. You will also have tests to check the overall health of your liver, kidneys, and blood cells. This study can not provide you with medical care, but study staff will refer you to other available sources of care.

If your Pap test result shows anything that is not normal, you will be referred for treatment at the [INSERT NAME OF PROVIDER/CENTER].

You will get counseling and testing for HIV. You will get free condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your own health care provider. You will get counseling and testing for other infections. If you have these infections, you will get medicine to treat them, if needed. You can bring your partner here for tests and treatment for these infections if he needs them.

If you become infected with HIV during this study, you will be referred for medical care. Medical care for HIV infection will not be a part of this study. You will need to get medical care for your HIV infection from your own health care provider.

## What Other Choices Do I Have Besides This Study?

You do not have to participate in this study, if you choose not to.

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

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places

where you can go for HIV counseling and testing. We will tell you about those places if you wish.]

Please talk to your doctor about these and other choices that may be available to you.

### **What About Confidentiality?**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- The U.S. Food and Drug Administration (FDA)
- U.S. National Institutes of Health (NIH)
- The local government or regulatory agency
- [INSERT NAME OF SITE] IRB
- Study staff
- Study monitors
- Ethics committees
- Drug companies supporting this study

[FOR US SITE INSERT: In addition to the efforts of the study staff to help keep your personal information private, a Certificate of Confidentiality has been obtained from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staff learn of possible child abuse and/or neglect or a risk of harm to yourself or others, they will be required to tell the proper authorities.]

### **What Are The Costs To Me?**

There is no cost to you for study related visits, study products, physical examinations, laboratory tests or other procedures.

### **Will I Receive Any Payment?**

You will receive payment for your time and effort in this study. You will receive [INSERT SITE-SPECIFIC AMOUNT OF MONEY] visits. You will also receive payment for activities affected by your participation in this study [SUCH AS CHILD CARE, TRAVEL, LOSS OF WORK TIME – SITES TO COMPLETE].



### **What Happens If I Am Injured?**

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. However, you or your insurance company may have to pay for this care. This institution or the U.S. National Institutes of Health (NIH) does not have a program to provide money for your injuries. You will not be giving up any of your legal rights by signing this consent form.

[SITES TO SPECIFY INSTITUTIONAL POLICY]

### **What Are My Rights As A Research Subject?**

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. You will be treated the same no matter what you decide. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

### **What Do I Do If I have Problems or Questions?**

For questions about this study or a research-related injury, contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research subject, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

**SIGNATURE PAGE**

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB/EC]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to take part in this study, please sign your name or make your mark below.

\_\_\_\_\_  
Participant's Name (print)

\_\_\_\_\_  
Participant's Signature and Date

\_\_\_\_\_  
Study staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study staff Signature and Date

\_\_\_\_\_  
Witness' Name (print)  
(As appropriate)

\_\_\_\_\_  
Witness's Signature and Date

**DIVISION OF AIDS  
HIV Prevention Trials Network (HPTN)  
SAMPLE INFORMED CONSENT FORM FOR  
THE STORAGE OF SPECIMENS OBTAINED WHILE PARTICIPATING IN  
A DAIDS-SPONSORED RESEARCH TRIAL  
FOR CHRONIC HEPATITIS B VIRUS INFECTED PARTICIPANTS**

**HPTN 059  
Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1%  
Tenofovir Gel**

**Final Version  
Version 1.0  
17 March 2005**

## **INTRODUCTION**

You have decided to take part in a Division of AIDS research study. While you are in this research study there may be some samples of blood taken from you that might be useful for future research. You are being asked to agree to the storage of these samples. This consent form gives you information about the collection, storage and use of your samples. The study staff will talk with you about this information. Please ask any questions, if you have some. If you agree to the storage of your samples, you will be asked to sign this consent form. You will get a copy to keep.

## **HOW WILL YOU GET THE SAMPLES FROM ME?**

The research doctors want to take extra blood samples from you during the study for storage. If you agree to these samples being taken, you will have about of blood (5 mL or one tablespoon) drawn [ OR LOCAL EQUIVALENT - SITE TO SPECIFY] at the Final Screening/Enrollment Visit, and Monthly Visits 3, 6, 7, 8, and 9. These additional samples collected during the study will be kept and used for future research.

## **HOW WILL YOU USE MY SAMPLES?**

Your samples will be used to look for evidence of the possible changes to the hepatitis B virus or damage caused by the infection, or your body's response to infection (such as examining cells, proteins, and other chemicals in your body) while you were using the study gel and after you stopped using the study gel. Tests may also include examining your genes (DNA), since they might affect your response to disease in important ways. Your genes might make you more or less susceptible to becoming infected, affect your responses to infection, or make your responses to treatment stronger or weaker. No other kinds of genetic test will be done by anyone on your stored specimens without first explaining the test to you and getting your permission.

The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored samples. This is because research tests are often done with experimental procedures, so the results from one research study are generally not useful for making decisions on managing your health. Should a rare situation come up where the researchers decide that one of the test results would provide important information 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 address and/or phone number. 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, address and phone number.

Your samples will not be sold or used directly to produce products that can be sold for profit. Research studies using your samples will be reviewed by the National Institutes of Health, and Ethics Committee, and a special committee at the researcher's institution (an Institutional Review Board).

#### **HOW LONG WILL YOU KEEP MY SAMPLES?**

There is no time limit on how long your samples will be stored.

#### **HOW WILL MY SAMPLES BE STORED?**

Your samples will be stored at special facilities that are designed to store samples safely and securely. 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 some access to your samples in order to store them and to keep track of where they are, but these people will not have information that directly identifies you. An Institutional Review Board will oversee the storage facilities to protect you and other research volunteers from harm.

#### **DOES STORAGE OF MY SAMPLES BENEFIT ME?**

There are no direct benefits to you. The benefit of doing research on stored samples includes learning more about HBV infection.

#### **WHAT ARE THE RISKS?**

There are few risks related to storing your samples. When tests are done on the stored samples 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?**

[Domestic Sites:] In order to keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records.

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with the research, such as the court system, about your participation. Also, any publication of the research will not use your name or identify you personally.

People who may review your records include: [INSERT NAME OF SITE] IRB, National Institutes of Health (NIH), study staff, study monitors, and their designees. Having a Certificate of Confidentiality does not prevent you from giving information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

Or

International Sites: In order to keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute privacy. Your personal information may be disclosed if required by law.

### **WHAT ARE MY RIGHTS?**

Allowing your samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study.

If you decide now that your samples can be stored for future research, you may change your mind at any time. You must contact your study doctor or nurse and let them know that you do not want your samples used for future research. Your samples will then not be used.

### **WHAT DO I DO IF I HAVE QUESTIONS?**

For questions about the storage of your samples, contact (*insert the name of the investigator*) at (*insert telephone number*).

For questions about your rights related to the storage of your samples for research, contact (*insert the name or title of person on the Institutional Review Board*) at (*insert telephone number*).

[INSERT SIGNATURE BLOCK AS REQUIRED BY LOCAL IRB/EC]

Please carefully read the statements below and think about your choice. No matter what you decide it will not affect your care, or your ability to participate in the study.

I agree to have additional blood samples taken for the purpose of storage and testing for future research related to HIV and HBV infection.

\_\_\_\_\_ Yes

\_\_\_\_\_ No

\_\_\_\_\_  
Participant's Name

\_\_\_\_\_  
Participant's Signature

Date

\_\_\_\_\_  
Study staff Conducting  
Consent Discussion

\_\_\_\_\_  
Study staff Signature

Date

\_\_\_\_\_  
Witness' Name  
(As appropriate)

\_\_\_\_\_  
Witness' Signature

Date